No. 17-1115

IN THE

United States Court of Appeals for the Federal Circuit

MERCK SHARP & DOHME CORP.,
Plaintiff-Appellant,

v.

HOSPIRA, INC.,
Defendant-Appellee.

Appeal from the United States District Court for the District of Delaware
Case No. 1:14-cv-00915, Judge Richard G. Andrews

BRIEF OF PLAINTIFF-APPELLANT MERCK SHARP & DOHME CORP.

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CERTIFICATE OF INTEREST

Counsel for the plaintiff-appellant certifies the following:

1. The full name of every party or amicus represented by me is:

   Merck Sharp & Dohme Corp.

2. The name of the real party in interest represented by me is:

   Merck Sharp & Dohme Corp.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

   Merck & Co., Inc.

4. The names of all law firms and partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

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STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule 47.5, appellant states as follows:

(a) There have been no previous appeals in this case.

(b) The same patents asserted in this case are being asserted in *Merck Sharp & Dohme Corp. v. Savior Lifetec Corp.*, Civil Action No. 5:15-cv-415, now pending in the U.S. District Court for the Eastern District of North Carolina.

JURISDICTIONAL STATEMENT

The District Court had jurisdiction under 28 U.S.C. §§ 1331 and 1338(a), and entered Final Judgment on October 24, 2016. Merck timely appealed on October 24, 2016. Fed. R. App. P. 4(a)(1)(A). This Court has appellate jurisdiction under 28 U.S.C. §1295(a)(1).

STATEMENT OF ISSUES

The District Court concluded that appellee Hospira had copied and infringed appellant Merck's U.S. Patent No. 6,486,150. The court found, however, that the asserted claims of the '150 patent were invalid for obviousness.

The questions presented are:

Did the District Court err in examining each step and substep of the '150 patent separately and in hindsight, rather than as a whole?

Did the District Court err in basing its obviousness determination on present-day hindsight, rather than from the perspective of what one skilled in the art would have known at the time of the invention?

Did the District Court err in failing entirely to consider one element of the claim when finding the patent obvious?

Did the District Court err in concluding that the patent was obvious even in the face of substantial objective evidence of nonobviousness, a portion of which was not even considered by the District Court?

INTRODUCTION

This case is about an elegant solution to a complex problem, which the District Court declared so simple in hindsight that it was unworthy of patent protection. The District Court was wrong.

It is a cardinal rule of patent litigation that a court assessing obviousness must consider the claimed invention as a whole, rather than disaggregating each of the patent's constituent steps and examining them separately. The District Court transgressed this fundamental rule when it declared Merck's '150 patent obvious – a result it reached only by viewing each step of the claimed process in isolation, breaking each step into several individual components, and then finding each of those components in the prior art or the knowledge of a skilled artisan.

The court compounded its error when it found that the recited *order* of steps in the '150 patent's claims was obvious, not in view of any teaching in the prior art, but on the basis of testimony explaining why, in view of what is known today, the recited order is critical. The fact that the sequence of steps is critical, however,

shows the value of the invention, not that it was obvious. That is why hindsight is a perilous thing when the validity of a patent is challenged. Conclusory testimony about what seems critical or logical today, untethered from any prior art and with the invention in mind, has no bearing on an obviousness determination.

The District Court also independently erred when it construed the asserted independent claim of Merck's '150 patent as containing a particular limitation, but failed to address that same limitation in its obviousness determination. The court's omission of that critical limitation was understandable—no prior art discloses it—but it was error nonetheless.

Each of these mistakes, alone or together, warrants reversal of the District Court's obviousness ruling. And reversal is all the more warranted because the objective evidence of *nonobviousness* here is so compelling. Merck's claimed invention was commercially successful. Hospira shamelessly copied it after repeatedly trying and failing to develop a noninfringing process. And (as Hospira appreciated by appropriating Merck's invention, but the District Court failed to acknowledge), the invention produced unexpected results. The District Court waved off all this objective evidence in favor of its own, erroneous, hindsight-heavy obviousness determination. That, like the rest, was reversible error.

The District Court's judgment should be reversed.

STATEMENT OF THE CASE

Background

1. The Instability of Ertapenem

The patents at issue in this litigation relate to a class of antibiotic drugs called "carbapenems." Carbapenems are part of a larger class of antibiotic compounds called "beta-lactams." Appx1210:12-19.

Carbapenems are broad-spectrum antibiotics, meaning that they are useful for treating a wide range of infections, including those caused by multiple types of bacteria. Appx1215:3-1216:2; Appx1225:9-1226:17. One of the first carbapenems to be commercialized was imipenem, which Merck developed and sold under the brand name Primaxin®. Appx1208:6-17; Appx1210:12-19; Appx3310.

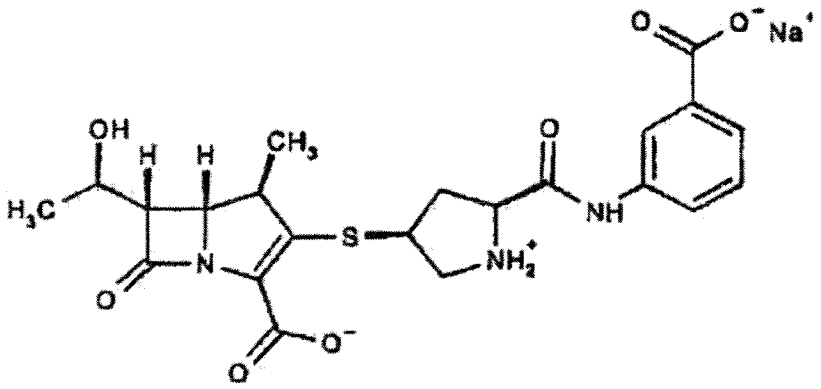
The carbapenem that is the subject of this litigation is ertapenem, which Merck sells under the brand name Invanz®. Invanz® is approved by the FDA for several indications, including intra-abdominal infections (such as infections associated with appendicitis), skin and skin structure infections, and urinary tract infections. Appx2894-2918 at Appx2896; Appx1221:1-1222:19. It is sold in single-dose vials as a lyophilized (freeze dried) powder, which is reconstituted into an aqueous solution by a health care provider and administered intravenously or by injection. Appx2896; Appx2918; Appx1211:19-23. All of the other carbapenems

in commercial use require multiple daily infusions. In contrast, ertapenem is administered only once per day, which provides significant cost and safety advantages and improves the effectiveness of treatment. Appx1211:24-1212:8; Appx1212:9-1215:2; Appx1224:24-1225:5; Appx27-28.

Ertapenem monosodium, the active ingredient in Invanz®, has the following structure (Appx1718):

2.2.1 Chemical Structure of Drug Substance

Figure 2.2.1.1: Chemical Structure of MK-0826 (L-749,345) as the Monosodium Salt



The ertapenem molecule is described and claimed in U.S. Patent No. 5,478,820 (Appx2948-2975), now expired. The '820 patent was assigned to Zeneca; but after Zeneca came to the conclusion that the development of a commercially viable ertapenem product would be very difficult, it subsequently licensed its patent rights to Merck. Appx23-24.

Ertapenem was difficult to develop into a commercially viable product because it is highly unstable at room temperature; it degrades into therapeutically

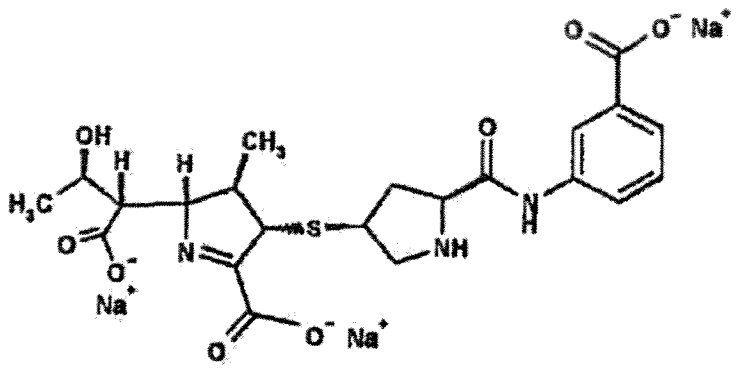
useless molecules. Appx5; Appx1063:4-12. In fact, even in dry form, ertapenem must be kept at temperatures below -20°C to avoid degradation; and when it is reconstituted into an aqueous solution, "it undergoes decomposition . . . far too rapidly for administration in a hospital setting." Appx278:20-279:1; Appx283:4-10. This instability was a "critical" obstacle that had to be overcome before ertapenem could be developed into a commercially viable drug. Appx282:16-23; Appx301:22-302:2; Appx1683. And that critical obstacle proved "very difficult" to overcome. Appx278:6-13. Zeneca "worked hard to come up with a stable formulation," Appx328:2-8, but failed to do so. Appx281:6-12; Appx284:12-18; Appx1246:15-16. It subsequently licensed the rights to the '820 patent to Merck.

The patents in suit are the results of Merck's concerted efforts to solve that stability problem and bring an ertapenem drug product to market.

2. The '323 Patent: Merck's Discovery of the Carbon Dioxide Adduct of Ertapenem

Ertapenem degrades in two different ways. The first is hydrolysis of the molecule's beta-lactam ring, the four-member ring (more a square) shown at the far left of the figure above. Ertapenem's beta-lactam ring is hydrolytically unstable, meaning that adding water to ertapenem powder causes the bonds of the ring to break, as shown below (Appx1722):

Figure 2.2.3.2: Structure of the Ring Open Hydrolysis Product (major degradation product) (L-744183)

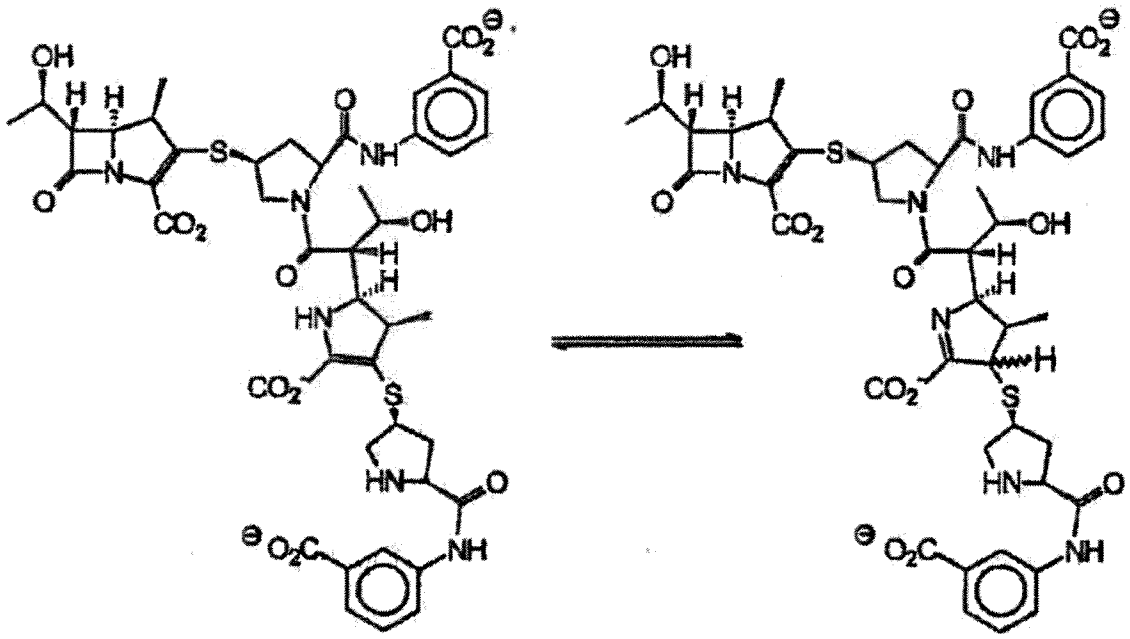


The molecules resulting from hydrolysis, called "ring open" degradants, are inactive; they have no antibiotic activity. Hydrolysis is a common problem for all compounds that, like ertapenem, have a beta-lactam ring. Appx5; *see also* Appx12 n.8 (noting that "all beta-lactams are hydrolytically unstable"). Most hydrolytically unstable drugs, including beta-lactams, exhibit the least degradation, and therefore have maximum stability, at a pH in the range of 3.5 to 5.5. Appx994:1-3; Appx996:11-14; Appx1043:17-20; *see also* Appx13 ("a pH about 4 . . . is within the range of maximum stability for hydrolytically unstable drugs like ertapenem").

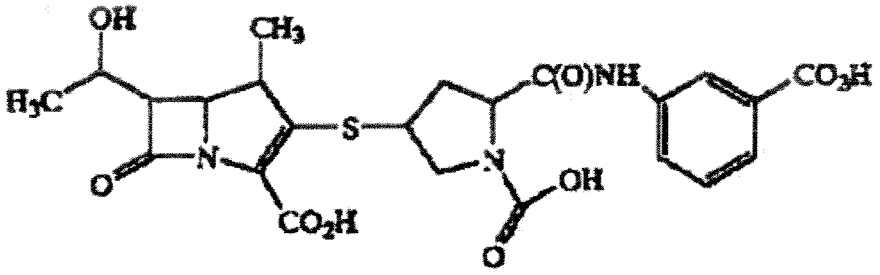
The second way ertapenem degrades is by "dimerization," in which two ertapenem molecules react with each other to form a larger molecule (a "dimer") with no antibiotic activity. Dimerization occurs when the pyrrolidine nitrogen of one ertapenem molecule—the nitrogen in the middle of ertapenem's molecular

structure in the first figure above—reacts with the beta-lactam ring of a second ertapenem molecule (Appx5-6; Appx1722):

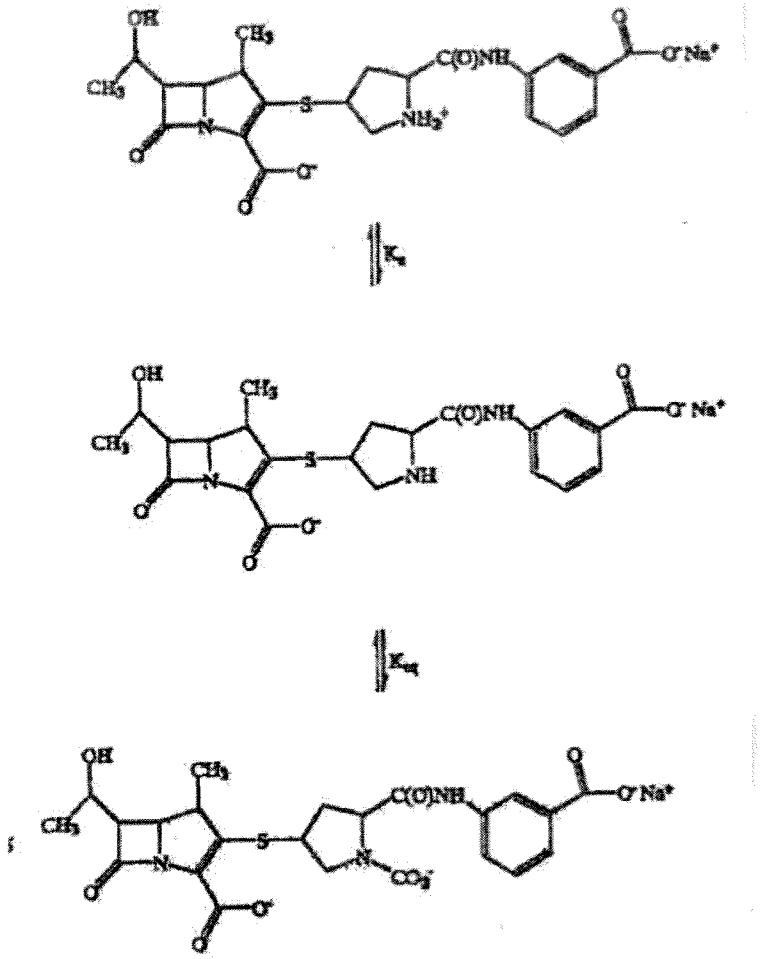
Figure 2.2.3.3: Structures of the Dimer Degradation Products (in equilibrium in solution)



Merck scientists attempting to develop a stable ertapenem formulation discovered "a very surprising result" (Appx289:8-21): formulating ertapenem with sodium bicarbonate ($NaHCO_3$) suppressed the dimerization rate, significantly improving the molecule's stability. Merck discovered that under certain conditions, ertapenem reacts with a carbon dioxide source (like sodium bicarbonate) to form a new molecule: the "carbon dioxide adduct" of ertapenem, Appx6, which has the following structure (Appx1335, Col. 2):



The District Court and certain witnesses sometimes referred to this as the "carbamate adduct" of ertapenem. In this case, the terms "adduct," "carbamate adduct," and "carbon dioxide adduct" all refer to the same thing. Appx6 n.3. In aqueous solutions where the carbon dioxide adduct is present, it exists in an equilibrium mixture with the unstabilized form of ertapenem (Appx1343):



The adduct stabilizes ertapenem by preventing the pyrrolidine nitrogen group of one ertapenem molecule from reacting with the beta-lactam ring of another ertapenem molecule, thereby inhibiting dimerization. Appx6.

Merck's scientists "had no reason to expect that bicarbonate would suppress the [formation] of dimers in solutions of ertapenem." Appx26 (citing Appx289:8-21). To the contrary, in fact; from their earlier experience with another carbapenem molecule, imipenem, they expected that the bicarbonate buffer would not be chemically reactive at all. Appx26 (citing Appx525:4-23). And although

the formation of carbamate adducts with other compounds was known, the prior art taught that it caused *degradation* of those other compounds – not increased stability. Appx1015:10-1016:12; Appx1017:13-1018:7; Appx1054:15-22; Appx1058:12-15; Appx1059:1-11; Appx1051:2-14; Appx1059:19-1060:19. Indeed, there was not a single reference in the literature prior to Merck's '323 patent where adduct formation was shown to stabilize a drug. Appx21; Appx1061:20-24; Appx987:5-10.

Merck's inventors discovered that the carbon dioxide adduct makes ertapenem stable at room temperature and allows it to retain its antibiotic activity in solution for several hours. Appx1063:5-12; Appx1068:4-8. Without that discovery, "ertapenem never would have become a commercial product." Appx301:15-302:2; *see* Appx24 ("The '323 patent solved this problem [*i.e.*, the instability of ertapenem] and enabled Plaintiff to market a stable product."); Appx1064:3-1065:17; Appx1068:9-1069:12; Appx1072:24-1073:18.

Merck's U.S. Patent No. 5,952,323 (the "'323 patent") (Appx1334-1341) discloses the carbon dioxide adduct of ertapenem. The claims asserted below were directed to a pharmaceutical composition comprising the carbon dioxide adduct (claim 2), and a method of stabilizing ertapenem by reacting it with carbon dioxide to form the carbon dioxide adduct (claims 4-6).

3. The '150 Patent: Development of a Commercially Viable Manufacturing Process

The Problem. The '323 patent disclosed the fundamental discovery that ertapenem could be stabilized by the formation of its carbon dioxide adduct. But it did not disclose a process that could manufacture formulations of the adduct at commercial scale with acceptable levels of degradants. Appx340:22-341:22. The development of such a process was "very challenging." Appx333:9-21.

The key challenge was that the two main types of undesirable degradants—ring open degradants and dimers—respond differently to pH. As a solution's pH *rises*, dimerization decreases, but ring open formation increases. When pH is *lowered*, the opposite reaction takes place: dimerization increases and ring open formation decreases. Appx345:14-346:16. Merck's scientists (including two of the '323 patent inventors) created this graph (Appx2548) to show the "divergent effect of pH" on dimers and ring open degradants (Appx1145:23-1149:2)[1]:

[1] The article from which this graph is taken (Appx2536-2553) is not prior art to the '150 patent. It was accepted for publication on June 19, 2001 (Appx2553), after the April 27, 2001, filing date of the '150 patent. It is nonetheless pertinent here because it illustrates the problem the '150 patent inventors confronted.

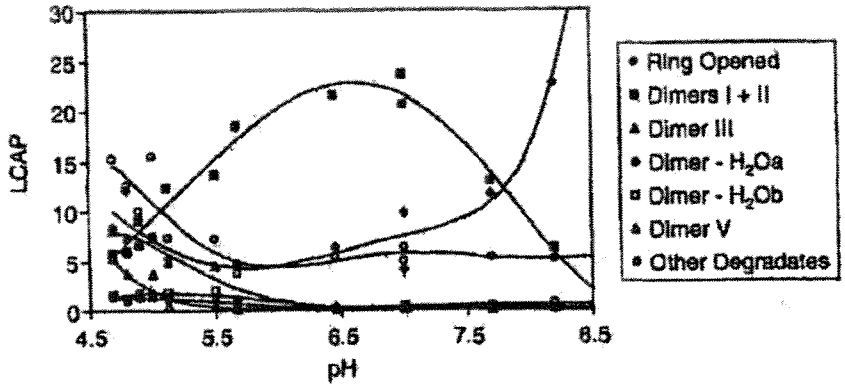


Figure 6. pH dependence of the degradation of ertapenem sodium. Sample concentration: 200 mg/mL. Degradation time: 24h.

The '323 patent solved one problem, because it showed how to minimize dimer formation through the formation of the carbon dioxide adduct. Appx289:8-21; *see also* Appx3225 and Appx3253 (Almarsson reference stating that the adduct inhibits dimerization). But because of the divergent effects of pH on ertapenem, solving the dimer problem created another problem in turn: the ideal pH range for formation of the carbon dioxide adduct—about 6 to about 9—would be expected to *increase* the *other* undesirable degradant, ring open hydrolysis products. This would lead a person of ordinary skill in the art to infer "that there's no aqueous solution of ertapenem that would have appropriate stability, so that's a significant challenge to making a formulated product. . . ." Appx1149:3-14. Hospira's expert admits that no prior art, including the '323 patent and Almarrson, addressed this problem. Appx739:4-20.

The Solution. The divergent effect of pH on dimers and ring open degradants was a "very challenging" problem that the inventors had to overcome in order to manufacture ertapenem on a commercial scale. Appx360:4-12; Appx361:10-16; Appx2398-2423. The Merck scientists recognized that any commercial-scale manufacturing process would have to minimize these two types of degradants, while also providing a finished product that would be stable for at least two years of shelf life, as well as stable enough upon reconstitution into solution that it could be administered intravenously or intramuscularly to patients. Appx334:19-335:8; Appx338:6-339:14. The development of a process meeting these goals took several years and extensive studies. Appx362:15-364:12; Appx1708-1772.

That work culminated in the '150 patent, the subject of this appeal. Appx1342-1353. The asserted claims of the '150 patent (claims 21-34) are directed to "[a] process for preparing a final formulation product of a compound of formula Ia, . . . or its pharmaceutically acceptable salt." Appx1351 at 18:11-23. Formula Ia is a generic chemical structure that encompasses the carbon dioxide adduct of ertapenem and other related molecules. Appx6. The process has three steps, as recited in independent claim 21:

(1) charging a solution of carbon dioxide source having a pH range of about 6.0 to about 12.0 into a reaction vessel;

(2) adding an effective amount of a mole ratio of a base and an active ingredient into the reaction vessel containing the solution of carbon dioxide source to maintain pH at about 6.0 to about 9.0 and a temperature range of about -3°C. to about 15°C.;

(3) lyophilizing the solution of Step (2) to yield the final formulation product of a compound of formula Ia with less than about 10% of moisture content.

The three steps – and their sequence – are "critical." Appx345:14-346:16. The first step, charging a solution of carbon dioxide source having a pH of about 6.0 to about 12.0 into a reaction vessel, creates a high-concentration "sea" of carbon dioxide source at the proper pH into which the active ingredient can be added. Appx1149:22-1150:18. This is done "so that upon adding the monosodium salt [of ertapenem], we would be able to form right away the carbon dioxide adduct and minimize degradation to form dimerization and also to form the ring degradants." Appx343:6-24.

The second step, "[a]dding an effective amount of a mole ratio of a base and an active ingredient into the reaction vessel . . . to maintain pH at about 6.0 to about 9.0 and a temperature range of about -3°C. to about -15°C.," ensures that there is enough ertapenem that is unprotonated (lacking a hydrogen ion) at the pyrrolidine nitrogen to react with the carbon dioxide source to form the adduct. The simultaneous addition of base maintains the pH in a range that permits the

adduct to form—thus minimizing dimerization—and keeping hydrolysis to a minimum – thus minimizing open ring degradation. Appx1150:19-1151:8.

Inventor Stelios Tsinontides explained Step (2) as "key to our invention," because "it prescribes a clear methodology" for adding sodium ertapenem in powder form into the solution along with sodium hydroxide to control the pH, "the window that we determine to provide us with the lowest level of degradation." Appx344:4-24. Dr. Tsinontides further explained that the "mole ratio" of base to active ingredient recited in Step (2) "is critical to ensure that . . . we have enough of the base to ensure that the pH of the solution does not shift . . . to move into areas where there will be either a dimer formation or a ring open." Appx345:1-13.

As Dr. Tsinontides explained, the *sequence* of Steps (1) and (2) was critically important as well, in order to overcome the "seesaw" effect of pH on dimers and ring open degradants (Appx345:14-347:16):

> Q. And what is the significance of the sequence of steps [(1) and (2)] . . . ?
>
> A. These steps were very critical and, of course, part of our invention in that they ensure that upon the API [active pharmaceutical ingredient] being introduced into the reaction vessel, it immediately is around an environment that allows it to form the adduct and thus minimizes the level of dimers being formed, and also minimizing all being formed, because as I indicated earlier, the pH as such that the formation of these two components are like a seesaw, is the pH drifts higher with the ring being formed. As the pH drifts lower because the API is

> acidic, then that causes a dimerization to kick on and dimers to be formed.
>
> So those two steps were very, very critical on how we designed them, and especially also on how we added the API and the sodium hydroxide solution, to ensure that upon the addition of the API, we would form minimum level of degradant.
>
> * * * *
>
> If you would add the API without adding the, without having the bicarbonate on the solution and adding the sodium hydroxide, the pH would drift low and start forming dimers. If you don't have a controlled addition of the base to the API, it is possible that the pH would drift high and start forming ring open degradants.

Finally, Step (3) of the claimed process "lock[s] in" the stability of the product to ensure that the formulation remains stable over the desired shelf life at room temperature. Appx348:1-19. With respect to the moisture level recited in Step (3) of the process (claim 21), the inventors found (Appx1749):

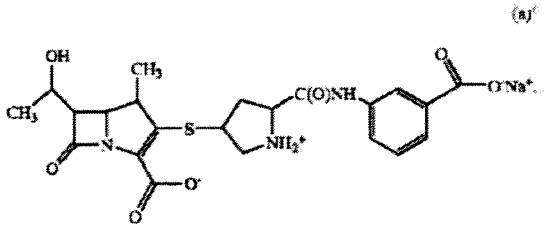
> The final product moisture is critical, as the solid stability of the product has been found to depend on moisture.
>
> * * * *
>
> Results of stability testing after 52 weeks at 25°C/60%RH, show . . . [a] substantial increase in ring-opened degradate formation . . . with . . . product moisture above 2.3% . . . . Based on this study, . . . it was recommended that initial moisture levels in MK-0826 for IV/IM injection, 1g/vial, be controlled to less than 2.3%w/w. . . .[2]

Dependent claims 22-34 of the '150 patent recite the conditions used in Merck's commercial manufacturing process "to insure that the process we employ

[2] "MK-0826" is ertapenem monosodium. Appx1718.

at the commercial stage produces the lowest amount of degradants . . ., so that we can produce a product with the highest . . . purity that will provide us with the needed stability of shelf life and upon reconstitution" (Appx352:2-23; Appx1155:14-1156:8):

> 22. The process of claim **21**, wherein the carbon dioxide source is selected from the group consisting of carbon dioxide, sodium bicarbonate. . . .
>
> 23. The process of claim **22**, wherein the carbon dioxide source is sodium bicarbonate.
>
> 24. The process of claim **23**, wherein the carbon dioxide source in Step (1) is present in an amount relative to the amount of active ingredient, wherein a mole ratio of carbon dioxide source to the active ingredient is about 0.5 to about 1.5.
>
> 25. The process of claim **24**, wherein the carbon dioxide source in Step (1) is present in an amount relative to the amount of active ingredient, wherein a mole ratio of carbon dioxide source to the active ingredient is about 0.8 to about 1.2.
>
> 26. The process of claim **25**, wherein the pH range in Step (1) is about 7.0 to about 9.0
>
> 27. The process of claim **26**, wherein a temperature range in Step (1) is about -3° C. to about 15° C.
>
> 28. The process of claim **27**, where the active ingredient is a compound of formula (a)',



[Formula (a)' is ertapenem. Appx47]

29. The process of claim **28**, wherein the base is selected from the group consisting of sodium hydroxide. . . .

30. The process of claim **29**, wherein the base is sodium hydroxide at a concentration range of about 1N to about 3N.

31. The process of claim **30**, wherein the effective amount of a mole ratio of a base to an active ingredient in Step (2) is about 0.7 to about 1.0.

32. The process of claim **31**, wherein the mole ratio of a base to an active ingredient in Step (2) is about 0.8 to about 0.9.

33. The process of claim **32**, wherein the pH range in Step (2) is about 7.0 to about 8.0.

34. The process of claim **33**, wherein the temperature range in Step (2) is about -1° C. to about 5° C.

Dependent claims 22-34 are the result of "numerous studies" by the inventors to achieve the lowest amount of both dimers and ring open degradants. Appx352:2-20; Appx363:8-23. Those studies are described in the "Invanz® Process Manual" dated May 11, 2001 (Appx1708-1772), just weeks after the application for the '150 patent was filed. Appx362:15-364:12. The dependent claims closely follow what the Process Manual identified as the "Critical Process Parameters" for the Invanz® commercial manufacturing process (Appx1744-1745):

1. The pH of the bicarbonate solution must be between the 8.1-8.5 at 0-5°C at the start of active addition. If the pH is above 8.5, do not proceed.

2. Addition of drug powder and of Sodium Hydroxide into the compounding vessel must be controlled. . . . [W]e have found

> that at a mole ratio of one mole of active per approximately 0.85 moles of NaOH (range of 0.8-0.9), it was possible to maintain pH during addition near the target of 7.5 at 0-5°C (range 7.2 to 7.8). . . .
>
> * * * *

4. Once the drug is added into the solution, the solution must be maintained below 10°C at all times. The recommended temperature range during manufacturing is between 0-5°C.

5. Use extreme care . . . to adjust the pH with the 2N NaOH solution after the drug addition. . . . . Confirm that the amount of NaOH added was within the typical range (0.8 to 0.9 mole equivalents). The final solution pH must be within the target range specified (7.2 to 7.8 at 0 – 5°C).

The Process Manual explains each of the foregoing process parameters and, hence, the limitations of the dependent claims.

With respect to the temperature of the sodium bicarbonate solution in Step (1) (claim 21 and dependent claim 27), the Process Manual explains that "[t]he target range of 1-10 °C allows faster dissolution of sodium bicarbonate. . . ." (Appx1745-1746).

With respect to the pH and mole ratios in Step (2) of the process (claim 21 and dependent claims 32 and 33), the Process Manual explains (Appx1726-1727):

> [S]tudies showed that, in order to maintain the solution pH close to the optimum of ~7.5 (range 7.2 to 7.8) during the drug addition process, both the NaOH solution and the active bulk drug addition rates into the solution should be controlled. . . . [T]he mole ratio of sodium hydroxide per mole of active in the final pre-lyophilized solution was ca. 0.85 (range 0.8 to 0.9) mole-equivalents. This

> amount has been shown to prevent a drift in pH . . . during the final volume adjustment . . . of the pre-lyophilized solution.

And with respect to the temperature recited in Step (2) (claim 21 and dependent claim 34), the Process Manual explains:

> The importance of temperature on the solution stability of the MK-0826 was described in the Manufacturing Stability Section. . . (see Table 2.3.2.5.2). (Appx1746).
>
> * * * *
>
> Table 2.3.2.5.2 shows that the higher the solution temperature the higher the rate of degradation, both in total dimer and ring open rates . . . . (Appx1742).
>
> * * * *
>
> **Table 2.3.2.5.2:** Total Degradation Rates of Final MK-0826 Pre-lyo Solution at 200mg/ml

Temperature, °C	**Degradation Rate, HPLC area %/hr**	**Degradation Rate, % claim/hr**
1	0.2*	0.3
5	0.4*	0.5
10	0.7**	1.0
15	1.0**	1.4
20	1.2**	1.8
23	1.4*	2.0

* Experimentally determined values
**Calculated values from curve fit equations of data points

Dr. Stahly explained that the temperature range in Step (2) reflects a balance between two competing interests: reducing degradation and forming the adduct. Lower temperatures reduce degradation, "but you also must realize that they also

want to form the adduct, and so the adduct reaction would be more accelerated at higher temperatures. So, again, there's a balance between the two things you're trying to have happen." Appx1189:2-1190:3.

The claimed three-step process of the '150 patent allows ertapenem to be sold as a finished drug product with long-term shelf life and enough stability upon reconstitution to be administered intravenously or intramuscularly to patients. Appx1160:18-1161:18. As inventor Tsinontides testified, "Merck would not have been able to commercialize this product if it were not [for] the process that we developed that is described in patent '150." Appx364:16-365:6.

The invention's ability to simultaneously reduce dimers and ring open degradants is illustrated in the '150 patent itself, Merck's NDA, and Hospira's ANDA process, which the court found copied the claimed invention of the '150 patent. Appx25; Appx39; Appx49. Examples 1, 2, and 3 of the '150 patent show that practicing the claimed method results in lyophilized cakes with low levels of moisture, dimers, and ring open degradants. Appx1154:10-1155:7; Appx1348-Appx1350 at 11:20-15:63. The degradant levels reported in those examples are similar to those set forth in Merck's NDA (Appx2647-2655; Appx2679; Appx2689) and Hospira's ANDA (Appx2840-2843) resulting "in cakes that had low enough levels of these degradants [dimers and ring open] that they met specifications." Appx441:2-443:4; Appx1156:9-1160:23. Those dimer and ring

open degradant levels are about one-half of the levels reported in Figure 6 of Appx2548, which displays the degradant profiles of ertapenem that was not made by the claimed process. Appx1156:9-1159:20.

The three-step process of the '150 patent supplied a "surprising" solution to the problem of the divergent effect of pH on dimers and ring open degradants. Appx1149:15-21. Indeed, even Hospira's expert at trial, Dr. Murgatroyd, grudgingly conceded that the process of the '150 patent was a "reasonably clever" way of reducing degradation products. Appx740:17-21.

And it is undisputed that the prior art does not disclose *any single one* of the three steps recited in claim 21 of the '150 patent—let alone the sequence of those steps. Appx739:4-20; Appx749:6-751:20; Appx755:10-758:11; Appx1165:19-1166:15; Appx1170:13-1171:3. Although the prior art (in the form of Merck's own '323 patent and the other reference relied upon by the District Court, WO 98/18800 (a published Merck patent application that the parties refer to as "Almarsson" (Appx3221-3273)), taught a pH range of about 6 to about 9 to form the carbon dioxide adduct, the only benefit of adduct formation disclosed in the prior art was a reduction in dimer formation (Appx3225). In fact, the prior art taught *away* from the inventors' solution, since it taught that hydrolysis of beta-lactams is minimized at a pH range of about 3.5 to 5.5, outside the ranges recited in the '150 patent claims. Appx993:12-994:3; Appx1043:1-24; *see also* Appx13

(noting that hydrolytically unstable drugs like ertapenem are most stable at pH of about 4).

The commercial embodiment of the '150 patent, Merck's Invanz® product, was highly successful. It generated sales of $1.8 billion in the U.S. alone from 2002 through 2014. Appx1235:20-1236:10; Appx1237:14-1238:11; Appx1239:12-1240:18; Appx1241:3-1242:8; Appx1657; Appx1658-1659; Appx1660. And its sales and market share increased consistently over that entire period despite the introduction of several major antibiotics in generic form during that period—showing that Invanz[®] had "prove[n] its value above and beyond much lower cost and more broadly available generics." Appx1238:12-1239:11.

The District Court Proceedings

Merck filed this patent case in July 2014, after receiving notice that appellee Hospira, a manufacturer of generic drugs, had filed an Abbreviated New Drug Application with FDA containing a "paragraph IV" certification alleging invalidity of the '323 patent, which is listed in the "*Orange Book*" in connection with Merck's Invanz®. Appx3502(¶7). The initial complaint asserted the '323 patent only. Merck subsequently filed an Amended and Supplemental Complaint asserting infringement of the '323 patent and the '150 patent, along with another patent not relevant here. Appx81-93. (The '150 patent was not listed in the

Orange Book because it claims a manufacturing process, not Merck's Invanz® or a method of using it. *See* 21 U.S.C § 355(b)(1).)

The case went to bench trial in April 2016. Hospira stipulated that its generic product would infringe claims 2 and 4-6 of the '323 patent if those claims were not invalid. Appx7. The District Court ultimately found the claims of the '323 patent valid, and thus infringed. Appx1-2.

That left the '150 patent—the patent covering the commercial-scale manufacturing process for a stable form of ertapenem. The key infringement issue as to that patent was how much carbon dioxide adduct needs to be present in "the final formulation product of a compound of formula Ia"—a limitation in Step 3 of the '150 patent.

At the Markman hearing, the District Court ruled that the "final formulation product" need not "be composed of pure carbon dioxide adduct," and expressed doubts as to whether the final formulation product must be "predominantly" in the form of the adduct. Appx221:13-18; Appx222:3-4. The Court announced a preliminary construction of that term, requiring the process to "'achieve the stabilized form of carbon dioxide adduct in the final composition'" by "'a high rate conversion' . . . from the carbapenem salt to the carbon dioxide adduct." Appx221:22-222:2. The "high rate conversion" language comes from Col. 9:13-17 of the '150 patent (Appx1347) ("The present process provide[s] a high rate

conversion from the alkali metal salt, such as monosodium salt of carbapenem to the carbon dioxide adduct and the low by-product formation, such as dimers and ring open compounds.").

At trial, both sides offered testimony on the meaning of "a high rate conversion" in the context of the '150 patent and whether Hospira's process satisfied it. Merck's witnesses pointed out that the '150 patent does not disclose any specific percentage of carbon dioxide adduct that must be in "the final formulation product of a compound of formula Ia." Appx410:19-23. Rather, it describes "a high rate conversion" in functional terms as providing "low by-product formation, such as dimers and open ring compounds." Appx1347 at 9:13-17. In view of these facts, Merck's witnesses showed that a skilled artisan would interpret the patent's disclosure of "a high rate conversion" of carbapenem salt to carbon dioxide adduct as the formation of a sufficient amount of adduct to achieve a product that has a low level of degradants – in other words, a stable product. Appx410:6-412:16; *see also* Appx338:6-340:3.

The only Hospira witness to opine on the meaning of "a high rate conversion" was Dr. Murgatroyd, who testified that it requires "a greater than 80 percent conversion" of active ingredient to carbon dioxide adduct. Appx663:16-24; *see also* Appx628:23-629:13. Dr. Murgatroyd admitted that there was no support for his "greater than 80 percent" number in the asserted claims, the patent

specification, or its prosecution history; nor could he cite any documents supporting his construction, or cite any example of a process that provides an 80 percent yield. Appx731:20-733:16. Moreover, Dr. Murgatroyd's construction is contradicted by the '150 patent claims themselves. Dependent claim 24 recites a carbon dioxide source to active ingredient mole ratio of about 0.5, and Dr. Murgatroyd admitted that that ratio could not possibly result in 80 percent conversion of carbapenem to adduct. Appx720:13-721:4.

The District Court therefore adopted Merck's construction and construed a "high rate conversion" as "a rate that results in a mixture of ertapenem and the carbamate adduct with the latter present in an amount sufficient to stabilize the formulation and provide for a low level of degradants." Appx37. The court recognized that by "degradants," the patent means dimers and ring open molecules. Appx35 (*citing* Appx1347 at 9:13-17); Appx36 (*citing* Appx1348-1350 at 12:20-15:63 tbls. 2, 4, and 7).

At trial, Hospira admitted that its manufacturing process satisfied every limitation of claims 21-34 of the '150 patent, except for its dispute about the meaning of the "final formulation product" limitation. Appx38. As noted above, Hospira argued that that limitation required at least 80 percent of the ertapenem to be in the form of the carbon dioxide adduct. The District Court rejected that construction, ruling instead that the limitation requires "a mixture of ertapenem

and the carbamate adduct with the latter present in an amount sufficient to stabilize the formulation and provide for a low level of degradants." Appx37. And Merck showed at trial that 53 to 65 percent of the ertapenem in Merck's commercial Invanz® product, and 48 to 60 percent of the ertapenem in Hospira's generic product, is in the form of the carbon dioxide adduct. Appx429:24-430:9; Appx431:5-432:2; Appx433:9-15. Since Hospira's product clearly constituted "a mixture of ertapenem and the carbamate adduct with the latter present in an amount sufficient to stabilize the formulation and provide for a low level of degradants," the court concluded that Hospira's product "will thus be made by a process which literally infringes the asserted claims of the '150 patent." Appx38.

The District Court also found that the invention of the '150 patent was a commercial success (Appx24; Appx39; Appx49), and that Hospira had copied the '150 patent (Appx25; Appx39; Appx49). During the development of its generic product, Hospira considered, as its "Second Alternate Strategy," "[u]sing different stabilizers other than carbon dioxide source (preferably Sodium chloride and/or Phosphate buffer)." Appx1689. Hospira tried no fewer than five formulations that would have avoided the '150 patent because they used stabilizers that were not carbon dioxide sources, but rejected all of them. Appx953:15-955:22; Appx2601-2612; Appx469:11-470:3; Appx1689. Instead, Hospira adhered to its "Primary Strategy," which was "to obtain a stable product (reversible carbon dioxide adduct)

using the process as per US Patent 6486150B2" – the '150 patent asserted here. Appx1689; Appx468:10-470:18; Appx25; Appx39; Appx49.

The District Court concluded, however, that the asserted claims of the '150 patent were invalid for obviousness. According to the court, Merck's own '323 patent and Merck's Almarsson patent application, coupled with the knowledge of a person of ordinary skill in the art, rendered the claims in the '150 patent obvious. Both references were of record during the PTO's examination of the '150 patent.[3]

As explained above (at 9-12), the '323 patent is directed to the carbon dioxide adduct of ertapenem, a pharmaceutical composition containing that adduct, and a method for stabilizing ertapenem by forming that adduct. The '323 patent does not disclose a commercial-scale manufacturing process for making a viable commercial pharmaceutical composition containing a mixture of ertapenem and its carbon dioxide adduct with low levels of both dimer and ring open degradants and having both long term stability and stability for administration to patients upon reconstitution. Appx1165:7-18; Appx748:21-749:5. Nor does the '323 patent address the problem of the divergent effect of pH on dimerization and the formation of ring open degradants, *i.e.*, hydrolysis, or how to solve that problem.

[3] Almarsson is cited as U.S. Patent No. 6,297,231, which the parties agree has the identical disclosure as WO 98/18800. Appx3501-3507 (¶58).

Appx739:4-20. In fact, the '323 patent never mentions dimerization or ring open degradation.

Nor does the '323 patent disclose any of the manufacturing steps of the claimed invention of independent claim 21, or the narrower manufacturing steps of dependent claims 27 and 30 to 34 of the '150 patent. Appx1165:7-18; *compare* Appx1334-1341 with Appx1351-1352 at 18:64-20:2. Specifically, the '323 patent does not disclose the manufacturing step of first charging a bicarbonate solution having a pH range of about 6 to about 12 into a reaction vessel as recited in step (1) of claim 21. Appx1165:19-24; Appx749:6-750:13. It does not disclose the manufacturing step of next charging into the bicarbonate solution active beta lactam carbapenem and a mole ratio of sodium hydroxide to maintain the pH within a pH range of about 6 to about 9 at a temperature of about -3°C. to about 15°C. as recited in step (2) of claim 21. Appx1166:1-10; Appx750:23-751:20. It does not disclose adding a base into a compounder to form carbon dioxide adduct; rather it discloses adding a base "to adjust the pH of the composition upon dilution or reconstitution." Appx1336 at 3:15-18; Appx1166:11-1167:2. It does not disclose lypohilizing the solution of step (2) to yield a final formulation product having both low dimers and ring open degradants, with less than 10% moisture content. Appx1167:21-1168:9; Appx754:13-755:9. And it does not disclose the additional narrowing limitations of dependent claim 27 (temperature in step (1)

about -3°C. to about 15°C.); claim 30 (base is sodium hydroxide at a concentration of about 1N to about 3N), claim 31 (mole ratio of base to active ingredient in step (2) about 0.7 to about 1.0); claim 32 (mole ratio of base to active ingredient in step (2) about 0.8 to about 0.9); claim 33 (pH in step (2) about 7.0 to about 8.0); and claim 34 (temperature in step (2) about -1°C. to about 5°C.). Appx1351-1352 at 18:64-20:2.

Almarsson, for its part, extends the '323 patent's invention of forming the carbon dioxide adduct beyond ertapenem to *other* carbapenem compounds, such as meropenem. Appx1197:2-12; Appx1202:6-19; Appx3221-3273. Almarsson also does not disclose a step-by-step manufacturing process for making a viable commercial pharmaceutical composition containing a mixture of ertapenem and its carbon dioxide adduct with both low dimer and ring open degradants having both long term stability and stability for administration to patients upon reconstitution. Appx1169:24-1170:12; Appx739:4-20. Nor does Almarsson address the problem of the divergent effect of pH on dimerization and ring open degradation, nor how to solve that problem resulting in a final formulation product with both low dimers and ring open degradants. Appx739:4-20. In fact, while Almarsson mentions forming the carbon dioxide adduct to reduce dimer degradation (Appx3252-3253), it never mentions ring open degradation or the simultaneous reduction of both dimer and ring open degradants. Appx1201:8-23. Almarsson also does not

disclose any of the manufacturing steps of the claimed invention of independent claim 21 of the '150 patent or the narrower manufacturing steps of dependent claims 27 and 30-34. Appx1169:24-1172:16; Appx755:21-756:19; Appx757:5-758:11; Appx761:5-17. And like the '323 patent, Almarsson does not disclose adding a base into a compounder to form carbon dioxide adduct; rather it discloses adding a base, such as sodium hydroxide "to adjust the pH of the composition upon dilution or reconstitution." Appx3244-3245; Appx1171:4-18; Appx758:12-17.

The District Court acknowledged (with some understatement) that the '323 patent did not "explicitly lay out the steps" claimed in the '150 patent. Appx33. It concluded, however, that a "skilled artisan" would have been able to piece together the '150 patent's steps, sequence, *and* details—although it took several pages just to explain how. Appx41-45. The court reached the same conclusion as to Almarsson, and on the same reasoning. Appx45-46.

The District Court entered final judgment on October 24, 2016. Appx1-3. This appeal followed.

SUMMARY OF THE ARGUMENT

I. It is undisputed that none of the process steps of the '150 patent is disclosed in the prior art. Nonetheless, the District Court ruled the claims invalid for obviousness over two references the PTO considered during the patent's examination, despite having found that Hospira infringed (and in fact copied) the

patent, and that the patent is commercially successful. It reached this result by breaking each claim step into several individual components, then finding each of those components in the prior art or within the general knowledge of a skilled artisan. But a court making an obviousness determination must consider the claimed invention as a whole, not piecemeal. The District Court ran afoul of this precept, as well as this Court's precedent forbidding the use of the claimed invention as a template to piece together the teachings of the prior art so that the claimed invention is rendered obvious. This flawed approach was an error of law that requires reversal of the judgment.

II. The District Court also committed reversible error when it found that the recited *order* of steps in the '150 patent claims would have been obvious. The court based this finding on the explanation by Merck's expert about why the order of steps is critical. But the notion that the sequence was important shows the *value of the invention*—not that it was *obvious*. After all, everyone agreed that the prior art did not teach the claimed sequence of steps. Testimony about what would be logical today, with the benefit of the invention and not based on any prior art, sheds no light on the actual question in the obviousness inquiry: what the prior art would have taught a person of ordinary skill at the time of the invention.

The District Court acknowledged that the prior art did not explicitly lay out the steps of the '150 patent, but concluded that the claims were obvious based on

"the knowledge, creativity, and common sense" of an ordinarily skilled artisan. The court's singular reliance on "common sense," however, went beyond anything that has ever been approved by this Court. Common sense is typically invoked to provide a motivation to combine—not to supply a missing claim limitation. As Hospira's expert repeatedly admitted, *none* of the '150 patent's process steps was disclosed in the prior art. That is why Hospira's expert could not combine known steps to arrive at the claimed invention; he instead had to reconstruct each claim step from scratch. And this reconstruction was not based on prior art references – the most reliable evidence of what would be commonsensical to a skilled artisan – but solely on the expert's hindsight opinions of what would have been logical to him. This error, too, requires reversal.

III. The District Court construed claim 21 as requiring the process to provide low levels of both dimers and ring open degradants, and required Merck to show that this limitation was satisfied to prove infringement. Merck did so. But when the court subsequently addressed obviousness, it failed to address that same limitation. It is (again) undisputed that no prior art discloses or even addresses this limitation. Because Hospira failed to prove by clear and convincing evidence that this limitation was disclosed in the prior art, the judgment should be reversed for this independent reason as well.

IV. Because independent claim 21 would not have been obvious, dependent claims 22-34 cannot have been obvious. There are additional grounds for overturning the judgment with respect to dependent claims 27 and 30-34. The narrowed ranges of various parameters in these claims are used in Merck's commercial manufacturing process and are the result of the inventors' extensive research efforts, with nothing in the prior art to guide them, to develop a process that produces a final formulation product with the lowest amount of degradants. Dr. Murgatroyd's conclusory testimony that those ranges were just "common sense" is irreconcilable with the extensive efforts that were required to arrive at them, and provides an insufficient foundation to support the court's judgment that the claims would have been obvious.

V. Hospira did not establish a prima facie case of obviousness, let alone a strong one. The District Court's reliance on precedent that objective evidence cannot overcome a strong prima facie case of obviousness was therefore misplaced. The objective evidence here is compelling. The court found that the claimed invention was commercially successful and that Hospira copied it. Indeed, Hopsira tried and failed to develop a noninfringing process. As this Court has noted, the argument that an invention was obvious carries diminished weight when offered by those who tried and failed to solve the same problem, and then promptly adopted the solution they are now denigrating. Further, the District Court failed to

acknowledge the evidence that the invention provided unexpected results, *viz.*, a solution to the problem of the divergent effect of pH on dimers and ring open degradants. Appropriate consideration of this objective evidence would have prevented the court from falling into "the trap of hindsight."

ARGUMENT

A patent shall not issue "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §103(a).

Obviousness is a question of law, which this Court reviews *de novo*, with underlying factual questions, which are reviewed for clear error following a bench trial. *Honeywell Int'l Inc. v. United States*, 609 F.3d 1292, 1297 (Fed. Cir. 2010).

Any obviousness inquiry, however, begins with a thumb on the scale in favor of the patent holder: "A patent shall be presumed valid." 35 U.S.C. §282. Obviousness must be proved by clear and convincing evidence. *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1367 (Fed. Cir. 2011). And a patent challenger has an all the more "enhanced burden" if the prior art relied upon to show obviousness was considered by the PTO during the patent's examination. *Id.*; *Metabolite Labs., Inc. v. Laboratory Corp. of Am.*, 370 F.3d 1354, 1368 (Fed.

Cir. 2004) (similarly noting the defendant's "even heavier burden" if PTO considered the reference).

I. THE DISTRICT COURT FAILED TO CONSIDER THE CLAIMED INVENTION AS A WHOLE.

The two references upon which the District Court's conclusion of obviousness was based, the '323 patent and Almarsson, were both of record during the examination of the '150 patent. "Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear and convincing standard came into play." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012). The District Court in this case reached the opposite conclusion—despite the more stringent burden of proof and despite the facts that Hospira tried and failed to find a noninfringing process of its own—because it made a fundamental error of law.

"[V]irtually all [inventions] are combinations of old elements." *Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698 (Fed. Cir. 1983). That is why §103(a) requires a court to evaluate whether the claimed invention *as a whole* would have been obvious. "The 'as a whole' instruction in title 35 prevents evaluation of the invention part by part. Without this important requirement, an obviousness assessment might break an invention into its component parts (A + B + C), then find a prior art reference containing A, another containing B, and

another containing C, and on that basis alone declare the invention obvious." *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1275 (Fed. Cir. 2004).

That is the mistake the District Court made here.

Independent claim 21 of the '150 patent recites three steps that must be carried out in their recited order to produce a "final formulation product" of the carbon dioxide adduct of ertapenem that is stable and has low levels of dimers and ring open degradants. It is undisputed that none of those three steps is disclosed in either of the references relied on by the District Court, the '323 patent and Almarsson. Hospira's own expert admitted (Appx658:4-6; Appx673:2-9):

> Q: Does the '323 patent teach any specific processing steps?
>
> A: No, it does not.
>
> * * * *
>
> Q. And does Almarsson, itself, describe any particular processing steps?
>
> A. Well, processing steps, no. He doesn't do processing steps. That's what he does. He gives the recipe and the end result is that a person of skilled in the art could work with a viable process to produce the final product formulation.

See also Appx748:21-749:5 (neither '323 patent nor Almarsson gives manufacturing steps); Appx766:13-17 (same); Appx768:12-769:5 (similarly acknowledging that the '323 patent and Almarsson "don't give you . . . a series of manufacturing steps," but only a "recipe"). Merck's expert confirmed that none of

the recited claim steps is disclosed in the '323 patent or Almarsson. Appx1165:19-1166:15; Appx1169:24-1171:3.

Because none of the recited claim steps appeared in the prior art, the District Court reached the conclusion it did on obviousness only by considering each step separately, and even then, breaking each of those steps into separate subparts to show that those *subparts* would have been obvious. For example, although all agreed there is no disclosure of step (1) ("charging a solution of carbon dioxide source having a pH range of about 6.0 to about 12.0 into a reaction vessel") in the prior art '323 patent, the District Court found:

> A skilled artisan, seeking to follow the teachings of the '323 patent, would begin a manufacturing process by creating a solution of carbon dioxide source at a pH of 6 to 9. Appx41-42.
>
> . . . by first adjusting the pH of the carbon dioxide source, ertapenem – which is sensitive to pH – may be added directly to a solution that is at the preferred pH. Appx42.

Even if these findings are accepted as true, they do not establish that step (1) of the '150 patent claims would have been obvious, let alone that the claimed invention of step (1) in combination with the other recited steps would have been obvious.

Step (2) recites: "adding an effective amount of a mole ratio of a base and an active ingredient into the reaction vessel containing the solution of carbon dioxide source to maintain pH at about 6.0 to about 9.0 and a temperature range of about -3°C. to about 15°C." All agreed there is no disclosure of this step in the

prior art. Instead, the District Court again broke it into separate components, focusing on each in isolation rather than the claim as a whole, and then found each component to be obvious:

> After creating a solution of a carbon dioxide source and water at a stable pH, a skilled artisan would add the active ingredient. Appx42.
>
> In doing so, a skilled artisan would seek to maintain the pH of ertapenem in solution . . . between about 6 to about 9, since that is precisely what was taught by the '323 patent. Appx42.
>
> The '323 patent explicitly notes that a base, such as sodium hydroxide, can be [] used to adjust the pH of the composition. Appx42.
>
> The '323 patent does not disclose the simultaneous addition of sodium hydroxide and ertapenem. A skilled artisan, however, would know that the monosodium salt of ertapenem sodium has a pH of about 5.5. . . . Thus, to counteract the acidifying effect of the ertapenem salt – and thus to keep the solution pH in the target range – a skilled artisan would simultaneously add a base, such as sodium hydroxide. Appx42.

The District Court then separately discussed the temperature range recited in step (2). After citing conclusory testimony from Hospira's expert, the court found that "Dr. Murgatroyd therefore opined that a person of ordinary skill in the art would have arrived at the claimed temperature range." Appx43 (citing Appx690:2-21 ("common sense to keep the temperature low"; -1°C. to 5°C. "would be sensible range that you would arrive at").

With respect to step (3) ("lyophilizing the solution of Step (2) to yield the final formulation product of a compound of formula Ia with less than about 10% of moisture content"), the District Court again broke the step into separate components, finding that "[t]he lyophilization process is important, as it removes the water from the composition, thereby stabilizing the remaining solid material." Appx43. The court further found that "a moisture content of 0.5 percent to 3.0 percent was common at the time of the invention," Appx43, and that "a skilled artisan would be able to achieve a moisture content below 10% with routine optimization." Appx44.

The District Court described the other reference relied upon by Hospira, Almarsson, as "very similar" to the '323 patent. Appx45; *see also* Appx672:22-673:1 (opining that the "recipe" described in Almarsson is "very similar, identical" to that of '323 patent). The court did not undertake a separate analysis of Almarsson, but summarily stated that "[j]ust as these disclosures rendered claim 21 obvious when taught by the '323 patent, they render claim 21 obvious here." Appx46.

The court did note that Almarsson contains a graph, not disclosed in the '323 patent, showing that the adduct reduces dimer formation and increases stability. Appx46. That Almarsson contains such a graph is true enough, as far as it goes; but that does not teach or suggest the three step manufacturing process of the '150

patent, or the reduction of both dimers and ring open degradants in the final formulation product. Almarsson teaches only that forming the adduct reduces dimer formation. Appx3225. It does not teach or suggest how to reduce ring open degradants. And in fact, with respect to the problem of ring open degradants, the prior art taught *away* from the claimed pH range of about 6 to about 9; it taught that the pH should be kept in a range of about 3.5 to 5.5 to minimize hydrolysis of the beta-lactam ring. Appx993:22-994:3; Appx996:11-14; *see also* Appx13 (hydrolytically unstable drugs like ertapenem most stable at pH of about 4). And the court's finding that Almarsson's data suggests "to keep the temperature low" (Appx46) is yet another example of considering one subpart of one claim step in isolation.

The District Court's dissection of the claimed invention into several component parts is an impermissible "form of hindsight reasoning, using the invention as a roadmap to find its prior art components." *Ruiz*, 357 F.3d at 1275. The court's mistake is not uncommon. *See, e.g.*, *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) ("It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious."); *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1139 (Fed. Cir. 1985) (criticizing use of claims as "blueprint" to

reconstruct claimed invention from prior art). But it is an error of law, and it requires reversal. *See Fritch*, 972 F.2d at 1266.

II. THE DISTRICT COURT'S FINDING THAT THE CLAIMED ORDER OF STEPS WOULD HAVE BEEN OBVIOUS IS IMPERMISSIBLY BASED ON HINDSIGHT.

Merck's expert Dr. Stahly testified that "the steps, the order of steps, the details of how each step is carried out" in the '150 patent are not presented in the '323 patent or Almarsson. Appx1165:7-18, Appx1169:24-1170:12. Dr. Stahly also explained why the recited order of steps discovered by the inventors is critical, and the problems not following that order would cause (Appx1151:9-1152:9):

> Q: What would happen if the active ingredient is added without the base?
>
> A: If the active ingredient was added to carbonate, that would drive the pH down, and it would lead to protonation of pyrrolidine amine, so that the adduct would not form, and it would also be in a region where hydrolysis would be faster.
>
> Q: And what would happen if the base were added to adjust the pH of the solution of the carbon dioxide source before the active ingredient is added?
>
> A: That would, that would drive the pH higher, and then when the active ingredient went in, it would, again, be in the region where hydrolysis would be faster than desired.
>
> Q: What would happen if all three components, the carbonate, active ingredient and base were added at the same time?
>
> A: That's really an uncontrolled situation. You've got different dissolution rates of the three components and many competing reactions. I would expect that there would be high levels of degradants from such an operation.

The District Court concluded from this "that the order of the steps would have been obvious to a person of skill in the art." Appx44. That, again, was error. Merely because a sequence discovered by the inventors is *critical* to an outcome does not mean it would have been *obvious*.

Dr. Stahly did not testify that the steps in their claimed order were disclosed or suggested by the prior art; indeed, he specifically testified that they were *not*. Appx1165:7-18. His testimony is simply that – testimony – about why the three steps of the claims must be carried out in the recited order. The court's conclusion that the order of steps would have been obvious in light of Dr. Stahly's testimony is therefore based on hindsight. *See, e.g., Zoltek Corp. v. United States*, 815 F.3d 1302, 1311 (Fed. Cir. 2016) (improper reliance on data from patent's own prosecution history to show obviousness); *InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1352 (Fed. Cir. 2014) (criticizing expert who "simply opined what a skilled artisan could accomplish" years after the invention date).

Hospira's expert Dr. Murgatroyd fell into that same hindsight trap again and again: Indeed, his testimony contained *so much* hindsight analysis that while it is quite unusual for a brief to quote an adverse expert at length, we do so here to prove our point.

Dr. Murgatroyd opined, for example, that "it would be sensible to make the carbonate solution . . . , and then to monitor the pH, . . . and then lyophilize,"

referring to comments regarding the general sequence of steps that he would use to manufacture a lyophilized product. Appx693:10-21. But that and much of the rest of Dr. Murgatroyd's testimony similarly focuses on what would be logical to him *today*, not in 2001, when Merck's scientists discovered and perfected the '150 patent's process, and certainly not with reference to any teaching in the prior art (Appx645:5-649:20):

> Q: Generally, what would be the first step in the manufacturing process of a lyophilized product?
>
> A: The lyophilized product – well, because lyophilization, certainly, in the pharmaceutical industry is from the aqueous phase, it would be to get the material into solution.
>
> Q: And how do you get a material into solution, generally?
>
> A: You would add the presumably solid to the solvent, to the material you dissolve it in, and stir it to get a homogeneous mixture.
>
> Q: And what is the most common vehicle or solvent in the manufacture of parenteral products?
>
> A: The keyword here is parenteral. And presuming that you say aqueous, it would be water for injection . . .
>
> Q: Besides the vehicle or the water for injection, what else would you consider adding to a parenteral manufacturing process?
>
> A: Something to – usually, pH is quite key. I would add, depending on where I was in terms of the pH scale, I would – I would after pH, both the protection of the active, and also I would try to get a neutral pH, because ultimately, it has to be injected into people.

* * * *

> Q: All right. If you were developing a process where you had to mix actives and excipients or more than one thing, how would you generally go about determining the order of addition on this?
>
> A: Again, looking back at the pH, I would prepare a solution with the correct – the water, or whatever, with the correct pH. I would then add the active into that pH controlled solution.
>
> * * * *
>
> Q: All right. After you have everything in solution, what do you do next in a parenteral manufacturing process?
>
> A: In a parenteral manufacturing process, you – you – I guess you stabilize it by drying it.
>
> * * * *
>
> Q: And how would you dry it?
>
> A: You would dry it by lyophilization.

Dr. Murgatroyd also testified that a person of ordinary skill could have taken the "recipe" disclosed in the '323 patent and developed a manufacturing process. He conceded that the '323 patent does not teach any specific manufacturing steps, but argued that this was not important; according to him, "once you have the recipe," "putting the steps together to come up with a final patient presentation would be what a pharmaceutical formulator would be doing every day of the week." Appx658:4-17. Here again, however, every comment regarding the steps that the skilled artisan would supposedly take, as opposed to the chemical

composition of the resulting product, is based not on the '323 patent or other prior art, but on Dr. Murgatroyd's piecemeal hindsight opinions (Appx659:13-663:15):

> Q: All right. And so if a person of ordinary skill in the art were to take the recipe disclosed in the '323 and set about to develop a manufacturing process, in 2001, in your opinion, what would be the first step a skilled artisan would do?
>
> A: In my opinion, the first step would be to get the carbon dioxide source at the correct pH into solution, ready to react with the carbapenem.
>
> * * * *
>
> Q: All right. And then after you had the bicarbonate and water in solution at pH six to nine, what would a skilled artisan do next?
>
> A: You would add the active. In this case, the ertapenem to have the reaction.
>
> Q: And what was – what issues would the person want to keep in mind as they're adding the ertapenem?
>
> A: Again, you would be monitoring the pH. . . .
>
> * * * *
>
> Q: Okay. And what about the temperature of this reaction? You mentioned controlling the temperature of the reaction vessel. How would you control it?
>
> * * * *
>
> A: I will control it as low as I could sensibly do without freezing it. . . .
>
> * * * *

> Q. Okay. And so after you've got the active, the sodium hydroxide and the bicarbonate in solution at appropriate pH, what would you do next?
>
> A. Stabilize it.
>
> Q. And what do you mean by stabilize it?
>
> A. Make sure that you didn't get any further degradation reactions. And, again, if you recall, what I did is, I said that in general things are more stable in solids than they are in solution, and so a reasonably obvious step would be to lyophilize it and get the final moisture down the lower level where stability is conferred.

Dr. Murgatroyd's testimony regarding the obviousness of the '150 patent claims over Almarsson is likewise rooted not in any teaching in Almarsson, but again on Dr. Murgatroyd's present-day, conclusory opinion regarding "what formulators would do every day of the week." Appx672:22-674:12. On re-direct, Dr. Murgatroyd admitted that Almarsson does *not* in fact make obvious "how to do it in terms of the steps" of the '150 patent claims, but rather "gives you all the information to enable you . . . to make the carbamate adduct." Appx768:23-769:5. He then ventured his "belief . . . that they could" form "the specific manufacturing step" claimed in the '150 patent. Appx770:6-1.

Dr. Murgatroyd's hindsight musings that Almarsson enables the carbamate adduct of ertapenem and that a skilled artisan "could form" a specific manufacturing step do not establish that Almarsson would have made the specific three-step process of the '150 patent claims obvious as of its invention date. *See*

InTouch, 751 F.3d at 1352 (expert "succumbed to hindsight bias" in testimony which "primarily consisted of conclusory references to her belief that one of ordinary skill in the art *could* combine these references, not that they *would* have been motivated to do so.").

Since there is no evidence that the claimed order of steps would have been obvious to a person of ordinary skill in the art as of the 2001 invention date of the '150 patent – as opposed to what Hospira's expert thought was "sensible" at the time of the trial – the District Court's conclusion "that the order of the steps would have been obvious to a person of skill in the art," Appx44, is reversible error.

The District Court acknowledged that "[t]he '323 patent may not explicitly lay out the steps claimed in the '150 patent," but concluded that the claims were obvious in view of "the knowledge, creativity, and common sense that an ordinarily skilled artisan would have brought to bear when considering combinations or modifications." Appx44-45 (quoting *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013)). The court's reliance on "common sense" as a ground for obviousness, however, went beyond anything that has been previously approved by this Court.

"[C]ommon sense is typically invoked to provide a known *motivation to combine*, not to supply a missing claim limitation." *Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1361 (Fed. Cir. 2016); *see also id.* at 1362 (noting that in the only

case identified "in which common sense was applied to supply a limitation that was admittedly *missing* from the prior art, the limitation in question was unusually simple and the technology particularly straightforward.") (discussing *Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1326 (Fed. Cir. 2009)). Further, when "common knowledge and common sense" are invoked, this Court "ha[s] emphasized the importance of a factual foundation to support a party's claim about what one of ordinary skill . . . would have known," and has noted that "perhaps the most reliable" form of evidence to provide that foundation is documentary evidence consisting of prior art in the area. *Randall*, 733 F.3d at 1362-63.

Here, as Hospira's expert repeatedly admitted, *none* of the steps of the claimed process of the '150 patent was disclosed in the prior art. *See supra* p. 38. Hospira's expert therefore did not combine known steps to arrive at the claimed invention. He reconstructed each limitation of each claim step from scratch, then pieced them together. His reconstruction, moreover, was not based on any prior art reference, but solely on his hindsight opinion of what would have been logical to him. Appx658:4-17 (not important that '323 patent does not disclose any specific processing steps because "once you have the recipe . . . putting the steps together . . . would be what a pharmaceutical formulator would be doing every day of the week"); Appx673:20-22 ("[I]t's pretty much what formulators do every day of the week. It's very, very standard steps."); Appx690:2-7 (although prior art does not

specify temperatures, "it is common sense to keep the temperature low to prevent any unnecessary or unwanted site reactions."); Appx693:10-21 (although prior art does not disclose order of steps, "[t]he order to me would be very logical. . . . To me it would be absolutely logical to do that.").

Repeated invocation of "the knowledge, creativity, and common sense" of a skilled artisan, with respect to every single step of claimed process *and* the order in which they are carried out, is not remotely enough to support an obviousness ruling. *See Arendi*, 832 F.3d at 1366 (Board improperly relied on "conclusory statements and unspecific expert testimony" in concluding that "it would have been 'common sense'" to perform one step of claimed method); *K/S HIMPP v. Hear-Wear Techs., LLC*, 751 F.3d 1362, 1365-66 (Fed. Cir. 2014) (error to accept "a conclusory assertion from a third party about general knowledge in the art *without evidence on the record*, particularly where it is an important limitation that is not evidently and indisputably within the common knowledge of those skilled in the art"). This case presents an especially stark example, because the testimony as to what would have been "logical" was not based on any prior art.

III. THE DISTRICT COURT FAILED TO CONSIDER THAT THE PRIOR ART DID NOT DISCLOSE OR SUGGEST A FINAL FORMULATION PRODUCT HAVING BOTH LOW DIMER AND RING OPEN DEGRADANTS.

As discussed above, the fighting issue for the parties on infringement had to do with the limitation "final formulation product of a compound of formula Ia." *See supra* pp. 25-27. The District Court construed that limitation to pertain to a product resulting from a "high rate conversion" of ertapenem to its carbon dioxide adduct, which the court in turn construed as "a rate that results in a mixture of ertapenem and the carbamate adduct with the latter present in an amount sufficient to stabilize the formulation and provide for a low level of degradants." Appx37. The District Court recognized that by "degradants," the patent means dimers and ring open molecules. Appx35 (*citing* Appx1347 at 9:13-17); Appx36 (*citing* Appx1348-1350 at 12:20-15:63 tbls. 2, 4, and 7). As noted previously, the ability of the claimed process to solve this problem is shown by the patent examples, Merck's NDA, and Hospira's ANDA, which the court found copied the claimed invention of the '150 patent. *See supra* pp. 22-23.

No one before the '323 patent even *recognized* the problem of the divergent effect of pH on dimers and ring open degradants. Appx739:4-20. In other words, the '323 patent solved one problem: it showed how to minimize dimer formation through the formation of the carbon dioxide adduct. But it created another

problem: the pH level necessary to stabilize dimerization *increased* open ring degradation, as shown by the graph at *supra* p. 13, and that in turn is what prompted the inventors to develop the manufacturing process embodied in the '150 patent. A person of ordinary skill in the art would have had no motivation to develop a process that overcame that problem. Merck's inventors did. *See Mintz,* 679 F.3d at 1377-78 (patent challenger "must prove by clear and convincing evidence that a person of ordinary skill in the . . . art[] at the time of the invention would have recognized the adherence problem recognized by the inventors and found it obvious to produce the . . . structure disclosed in the . . . patent to solve that problem"); *In re Omeprazole Patent Litigation*, 536 F.3d 1361, 1380 (Fed. Cir. 2008) (claims reciting a multi-component drug formulation including a subcoating to prevent reaction between drug core and enteric coating unobvious where prior art did not disclose problem of that reaction and therefore person of ordinary skill would have had no reason to apply a subcoating).

Hospira's expert Dr. Murgatroyd conceded that the prior art does not address the problem of the divergent effect of pH on dimerization and ring open degradants. Appx739:14-20. Indeed, the prior art actually teaches away from the '150 patent's solution to this problem. *See supra* pp. 23-24, 42. Because there is no prior art of record that discloses—or even addresses—one of the claim limitations as construed by the District Court (a final formulation product with low

dimers and ring open degradants), the court erred in concluding that Claim 21 was a mere "general recitation of routine manufacturing steps which would have been obvious to one of ordinary skill in the art." Appx45.

The district court in *Honeywell Int'l Inc. v. United States*, 609 F.3d 1292 (Fed. Cir. 2010), committed a similar error: it correctly construed claim element "(a)(3)" as imposing a certain requirement for infringement, but *omitted* that requirement when it found that element (a)(3) was disclosed in the prior art. *Id.* at 1299-1301. This Court concluded that the trial court had "committed clear error in finding that [a cited reference] discloses element (a)(3)," and that given the defendant's corresponding "failure to prove that the cited references disclose element (a)(3), [it] failed to carry its burden of proving . . . that the claimed invention would have been obvious." *Id.* at 1300-01. Hospira's failure to prove that the prior art disclosed the claim requirement of providing low levels of both dimers and ring open degradants is an independent reason why the judgment of obviousness should be reversed.

IV. THE RECORD DOES NOT SUPPORT A JUDGMENT THAT THE DEPENDENT CLAIMS WOULD HAVE BEEN OBVIOUS.

For much the same reasons that require reversal of the District Court's conclusion that independent claim 21 of the '150 patent was obvious, its conclusion that dependent claims 22-34 are invalid for obviousness must be

reversed as well. *In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988) ("Dependent claims are nonobvious . . . if the independent claims from which they depend are nonobvious.").

There are additional grounds for overturning the judgment with respect to dependent claims 27 and 30-34:

> 27. The process of claim **26**, wherein a temperature range in Step (1) is about -3°C to about 15°C.
>
> 30. The process of claim **29**, wherein the base is sodium hydroxide at a concentration range of about 1N to about 3N.
>
> 31. The process of claim **30**, wherein the effective amount of a mole ratio of a base to an active ingredient in Step (2) is about 0.7 to about 1.0.
>
> 32. The process of claim **31**, wherein the mole ratio of a base to an active ingredient in Step (2) is about 0.8 to about 0.9.
>
> 33. The process of claim **32**, wherein the pH range in Step (2) is about 7.0 to about 8.0.
>
> 34. The process of claim **33**, wherein the temperature range in Step (2) is about -1° C. to about 5° C.

The District Court's conclusions as to each of these dependent claims were impermissibly cursory—because the District Court improperly relied (again) on nothing more than the expert's conclusory opinion about what would be obvious to him.

The District Court concluded that claim 27 would have been obvious for the same reasons the claimed temperature range in step (2) would have been obvious.

Appx47. But the testimony regarding that temperature range amounted to nothing more than Dr. Murgatroyd opining that it would make sense to him as of the time of the trial, without basis in the prior art. *See supra* p. 40. The only additional testimony from Dr. Murgatroyd regarding to claim 27 was equally conclusory. Appx682:14-683:1 (offering the view that "it would be pretty obvious that you keep the temperature as low as possible above freezing in order to slow down any necessary or for any side reactions"). Contrary to Dr. Murgatroyd, Merck's expert explained that the recited temperature range reflects a balancing of the need to reduce degradation (suggesting lower temperatures) and the need to form the adduct (accelerated at higher temperatures). Appx1189:2-1190:3.

With respect to claim 30, the District Court acknowledged that the 1N to 3N base concentration was not disclosed in the '323 patent or Almarsson, but relied on Dr. Murgatroyd's testimony that the recited concentrations "were commonly used by persons of ordinary skill, in order to minimize pockets of extreme pH." Appx48. But—again—an expert's view that that aspect of the process "is a common sense thing" is simply not an appropriate foundation on which to rest an obviousness ruling.

Similarly, with respect to claims 31 and 32, Dr. Murgatroyd admitted that the recited mole ratios of base to active ingredient are not disclosed in the prior art, but opined that this does not matter because "neutralizing an acid with a base,

which is effectively what you're going to do, would effectively automatically generate that range, that mole ratio." Appx686:10-24. He elaborated that "when you stay within your target pH, . . . the end result would be the correct mole ratio," *i.e.*, the ratios recited in claims 31 and 32. Appx687:1-688:7. But his conclusion that "the end result would be the correct mole ratio"—referring to the recited claim limitation—is yet another example of using the claimed invention as a template to render its own claims obvious. *Interconnect*, 774 F.2d at 1139. And his cavalier assertion that one would simply "automatically" generate the recited mole ratios is belied by the evidence that the inventors worked extensively to develop them. Appx1708-1772, discussed at pp. 19-21, above.

As for dependent claims 33 and 34: the pH range of claim 33, according to Dr. Murgatroyd, is obvious because the chemistry "would be reasonably simple" and "a person of ordinary skill in the art would do experiments to find the optimum pH." Appx688:16-689:13. And the temperature range of claim 34 was just "common sense" that "would be [a] sensible range that you would arrive at. My suspicion is, it would go straight down to something in that range. . . . It's very common." Appx689:22-690:21. Hindsight is always 20/20; and elegant solutions to difficult problems always look like common sense when they are solved. The District Court's reliance on mere hindsight and proclamations of "common sense," without basis in the prior art, was fundamentally erroneous.

V. THE COURT GAVE INADEQUATE WEIGHT TO OBJECTIVE EVIDENCE OF NONOBVIOUSNESS.

"Secondary considerations, when present, must be considered in determining obviousness." *Ruiz*, 234 F.3d at 667. The District Court dismissed all of the objective evidence of nonobviousness, however, concluding that it "cannot overcome a strong prima facie case of obviousness." Appx49 (quoting *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)). For all of the reasons discussed above, however, Hospira did not establish a prima facie case of obviousness, let alone a strong one.

And the objective evidence of nonobviousness here is compelling. Hospira tried at least *five* alternative formulations in an attempt to avoid infringing the '150 patent, but ultimately abandoned all of them and elected to adhere to its "Primary Strategy": "to obtain a stable product (reversible carbon dioxide adduct) using the process as per [Merck's '150 patent]." Appx1689; Appx953:15-955:22; Appx2601-2612; Appx468:10-470:18; Appx25; Appx39; Appx49. Hospira's herculean efforts are telling: "[T]he litigation argument that an innovation is really quite ordinary carries diminished weight when offered by those who had tried and failed to solve the same problem, and then promptly adopted the solution that they are now denigrating." *Mintz*, 679 F.3d at 1379-80 (quoting *Heidelberger*

Drucksmaschinen AG v. Hantscho Comm'l Prod., Inc., 21 F.3d 1068, 1072 (Fed. Cir. 1994)).

The District Court also concluded that Hospira copied the '150 patent (Appx25; Appx39; Appx49) and that the claimed invention had been a commercial success (Appx24; Appx39; Appx49). But it failed to acknowledge or address the evidence that the invention provided unexpected results. This invention plainly did: it solved the problem of the divergent effects of pH on dimers and ring open degradants, Appx1149:3-21, and it did so in an unexpected way: after all, the prior art taught away from the claimed method. *See supra* pp. 23-24, 42. Even Hospira's expert Dr. Murgatroyd was constrained to concede that the claimed process was a "reasonably clever" way of reducing degradation products. Appx740:17-21. Quite so. It was "reasonably clever" enough to receive a patent, and "reasonably clever" enough for Hospira to slavishly copy it.

Courts assess objective evidence of nonobviousness to ensure that they do not fall prey to "'the trap of hindsight.'" *Mintz*, 679 F.3d at 1379 (quoting *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 960 (Fed. Cir. 1986)); *see In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012) (calling secondary considerations a "check against hindsight bias"). The District Court paid too little heed to the significant

objective evidence of nonobviousness here – and far too much heed to hindsight. Its obviousness ruling should be reversed.

CONCLUSION

For all of the foregoing reasons, the District Court's judgment should be reversed.

Respectfully submitted,
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ADDENDUM

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MERCK SHARP & DOHME CORP.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 14-915 (RGA)
	)	CONSOLIDATED
HOSPIRA, INC.,	)	
	)	
Defendant.	)	

[PROPOSED] FINAL JUDGMENT

This patent infringement action was brought by Plaintiff Merck Sharp and Dohme Corp. ("Merck") against Defendant Hospira, Inc. ("Hospira"), alleging Hospira's Abbreviated New Drug Application ("ANDA") No. 206480 infringed U.S. Patent Nos. 5,952,323 (the "'323 Patent"), 6,486,150 (the "'150 Patent") and 6,548,492 (the "'492 Patent"). On November 17, 2014, Hospira stipulated that ANDA No. 206480 infringes claims 2 and 4-6 of the '323 Patent, if those claims are not invalid or unenforceable (D.I. 34). On March 18, 2016, a Stipulation of Partial Dismissal of Claims with respect to the '492 Patent was filed (D.I. 187). The Court conducted a bench trial from April 18 to 21, 2016 on the issues of validity of the asserted claims 2 and 4-6 of the '323 Patent and the validity and infringement of the asserted claims 21-34 of the '150 Patent.

Having considered the documentary evidence and testimony, and having reviewed the parties' post-trial briefs, for the reasons set forth in the Court's *Markman* Order dated July 30, 2015 (D.I. 137), and the Trial Opinion dated October 7, 2016 (D.I. 220), **IT IS ORDERED AND ADJUDGED** that:

1. Judgment is entered in favor of Merck and against Hospira that claims 2 and 4-6 of the '323 Patent are not invalid as anticipated under 35 U.S.C. § 102, not invalid for

obviousness under 35 U.S.C. § 103, and not invalid for lack of written description under 35 U.S.C. § 112.

2. In view of the judgment for Merck on the validity of the asserted claims of the '323 Patent and the parties' aforementioned stipulation that the ertapenem product that is the subject of ANDA No. 206480 infringes claims 2 and 4-6 of the '323 Patent, judgment is entered in favor of Merck and against Hospira that the commercial manufacture, use, offer for sale, sale, in the United States and/or importation into the United States of the ertapenem product that is the subject of Hospira's Abbreviated New Drug Application ("ANDA") No. 206480 would infringe claims 2 and 4-6 of the '323 Patent.

3. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any final approval by the United States Food and Drug Administration of Hospira's ANDA No. 206480 shall be a date not earlier than November 15, 2017, the date of expiration of the '323 Patent together with the period of pediatric exclusivity awarded to Merck under 21 U.S.C. § 355a.

4. Pursuant to 35 U.S.C. § 271(e)(4)(B), Hospira and its officers, agents, employees and attorneys, and those who are in active concert or participation with those who receive actual notice of this Final Judgment by personal service or otherwise, are hereby enjoined from engaging in the commercial manufacture, use, offer for sale, sale, in the United States and/or importation into the United States of the ertapenem product that is the subject of Hospira's ANDA No. 206480 until May 15, 2017, the expiration date of the '323 Patent.

5. Judgment is entered in favor of Hospira and against Merck that asserted claims 21-34 of the '150 Patent are invalid as obvious under 35 U.S.C. § 103.

6. Judgment is entered in favor of Merck and against Hospira that claims 21-29 of the '150 patent are not invalid for lack of novelty under 35 U.S.C. § 102.

7. Judgment is entered in favor of Merck and against Hospira that the commercial importation into the United States and sale in the United States of the ertapenem product that is the subject of ANDA No. 206480 would infringe claim 21-34 of the '150 patent if those claims were not invalid under 35 U.S.C. § 103.

Dated this 24th of October, 2016

Richard G. Andrews
United States District Judge

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MERCK SHARP & DOHME CORP.,

Plaintiff,

v.

HOSPIRA INC.,

Defendant.

Civil Action No. 14-915-RGA

TRIAL OPINION

Jack B. Blumenfeld, Esq., Derek J. Fahnestock, Esq., Morris, Nichols, Arsht & Tunnell LLP, Wilmington, DE; Tony V. Pezzano, Esq., Michael P. Dougherty, Esq., Hogan Lovells LLP, New York, NY, attorneys for Plaintiff Merck Sharp & Dohme Corp.

Melanie K. Sharp, Esq., Samantha G. Wilson, Esq., Young, Conaway, Stargatt & Taylor LLP, Wilmington, DE; Thomas J. Meloro, Esq., Christopher J. McNamara, Esq., Michael W. Johnson, Esq., Tara L. Thieme, Esq., Willkie Farr & Gallagher LLP, New York, NY, attorneys for Defendant Hospira Inc.

October 7, 2016

ANDREWS, U.S. DISTRICT JUDGE:

Plaintiff brought this patent infringement suit against Defendant on July 11, 2014. (D.I. 1). On May 29, 2014, Defendant informed Plaintiff that it had filed an ANDA, seeking approval to engage in the commercial manufacture, use, or sale of generic versions of Plaintiff's Invanz product. (D.I. 191, Ex. 1 ¶ 15). Plaintiff alleges that this ANDA filing infringes U.S. Patent Nos. 5,952,323 ("the '323 patent") and 6,486,150 ("the '150 patent") (collectively, "the patents-in-suit").

The patents-in-suit, and Plaintiff's Invanz product, relate to an antibiotic called ertapenem. Ertapenem is a member of a class of antibiotics called carbapenems. Ertapenem is administered by intravenous, subcutaneous, or intramuscular injection. Ertapenem is highly unstable. (Tr. 760:5-13).[1] Specifically, ertapenem may undergo two types of degradation reactions that are relevant to this case: hydrolysis and polymerization. (Tr. 761:1-3, 856:7-13).

Hydrolysis, specifically "ring-opening hydrolysis," is a problem for all compounds which, like ertapenem, have a beta-lactam ring. (Tr. 88:11-18). Hydrolysis occurs when water breaks open the beta-lactam ring, thereby rendering the molecule ineffective. (Tr. 397:19-398:8, 765:21-24, 855:18-856:13). While beta-lactams may undergo hydrolysis at any pH, hydrolysis occurs more readily as pH values move away from neutral—i.e., as the solution becomes increasingly basic or acidic. (Tr. 89:2-19, 90:13-17, 397:21-398:20, 761:22-762:2, 924:7-17).

Polymerization occurs when two or more molecules of the same type react with each other to form what is called a polymer. Dimerization is polymerization when only two molecules are involved. The resulting molecule is called a "dimer." (Tr. 761:13-16). When dimerization occurs, the original molecules have been fundamentally changed. (Tr. 765:21-

[1] References to the trial transcript are identified as "Tr." The trial transcript is filed on the docket at D.I. 212 to D.I. 215.

766:5). Dimerization of ertapenem occurs when the pyrollidine amine of one ertapenem molecule reacts with the beta-lactam ring of another ertapenem molecule to form a dimer. (Tr. 855:1-3).

Ertapenem was first claimed in U.S. Patent No. 5,478,820 ("the '820 patent"), which is not asserted here. Rather, this case concerns the '323 and the '150 patents. The asserted claims of the '323 patent[2] are directed to a stable pharmaceutical composition containing ertapenem, and to a method of stabilizing ertapenem. (PTX 1 at 9:14-28, 10:31-64).

The '323 patent teaches that by increasing the pH of the ertapenem compound—through the addition of carbonate or bicarbonate—the hydrolysis reaction that tends to occur at low pH ranges can be avoided. While elevating the pH may increase the likelihood that polymerization occurs (Tr. 817:2-16), the '323 patent explains that this polymerization reaction can be prevented through the formation of a carbamate adduct ("the adduct").[3] (Tr. 806:19-807:20). The adduct is formed when ertapenem reacts with a carbon dioxide source—in this case, carbonate or bicarbonate—at a pH range of about 6.0 to 9.0. (Tr. 762:19-763:3). When the carbamate adduct forms, at ertapenem's pyrollidine ring, the pyrollidine nitrogen is no longer reactive, and therefore cannot react with the beta-lactam ring, thereby preventing the polymerization reaction. (Tr. 91:8-18, 762:11-18).

The asserted claims of the '150 patent[4] are directed to "[a] process for preparing a final formulation product of formula Ia, . . . or its pharmaceutically acceptable salt." (PTX 2 at 18:11-23). Formula Ia is a generic chemical structure which encompasses the carbamate adduct of ertapenem and other related carbapenem molecules. (Tr. 113:9-19, 119:5-11).

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[2] Plaintiff asserts independent claims 2 and 4 and dependent claims 5 and 6.
[3] The carbamate adduct is a particular form of ertapenem. In this opinion, the adduct may be referred to as the adduct, the carbamate adduct, or the carbon dioxide adduct.
[4] Plaintiff asserts independent claim 21 and dependent claims 22-34.

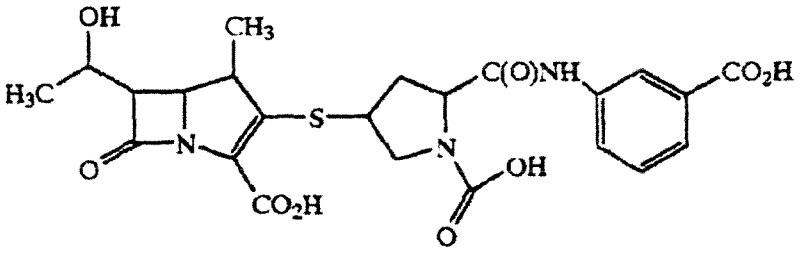
The Court held a bench trial on April 18-21, 2016. Defendant concedes that its generic product would infringe claims 2 and 4-6 of the '323 patent, if those claims are not held invalid or unenforceable. (D.I. 191, Ex 1 ¶ 18). Defendant argues that all of the asserted claims of the '323 patent are invalid as obvious and anticipated, and that asserted claims 4-6 are invalid for lack of written description. Defendant contests infringement as to the '150 patent, and asserts that it is invalid on grounds of anticipation and obviousness.

I. '323 PATENT

Independent claim 2 of the '323 patent reads:

> A pharmaceutical composition which is comprised of a compound represented by formula II:

II

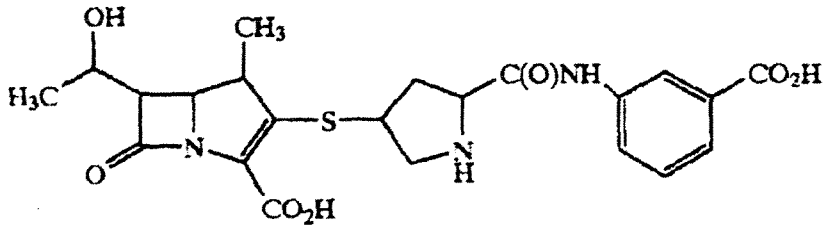


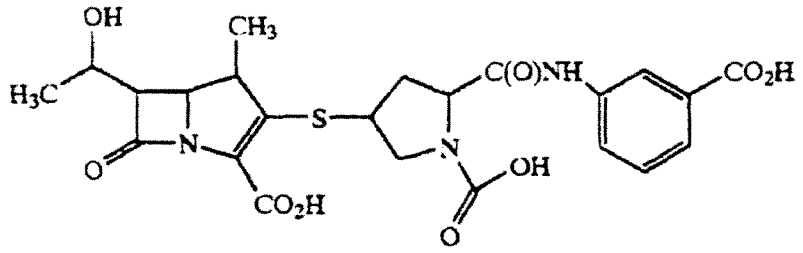
> or a pharmaceutically acceptable salt, prodrug or hydrate thereof, in combination with a pharmaceutically acceptable carrier.

(PTX 1 at 9:14-28). Independent claim 4 reads:

> A method of stabilizing a carbapenem of the formula I:

I



> or a pharmaceutically acceptable salt, prodrug or hydrate thereof, comprising adding to the compound a sufficient amount of a carbon dioxide source to form a compound of formula II:
>
> II
>
> 
>
> or a pharmaceutically acceptable salt, prodrug or hydrate thereof.

(*Id.* at 10:30-57). Dependent claim 5 limits the carbon dioxide source to "carbon dioxide, sodium carbonate and sodium bicarbonate," while dependent claim 6 further limits the carbon dioxide source to "sodium carbonate and sodium bicarbonate." (*Id.* 10:58-64).

A. Anticipation

i. Legal Standard

A patent claim is invalid as anticipated under 35 U.S.C. § 102 if "within the four corners of a single, prior art document . . . every element of the claimed invention [is described], either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1346 (Fed. Cir. 2009) (alterations in original). "Thus, a prior art reference without express reference to a claim limitation may nonetheless anticipate by inherency." *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1375 (Fed. Cir. 2005). To establish inherency, "prior art [must] necessarily function[] in accordance with, or include[], the claimed limitations." *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999). In other words, "[i]nherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." *Trinitec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295

(Fed. Cir. 2002) (quoting *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)). Inherent anticipation does not, however, "require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure." *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). "[T]he party asserting invalidity due to anticipation must prove anticipation, a question of fact, by clear and convincing evidence." *Orion IP, LLC v. Hyundai Motor Am.*, 605 F.3d 967, 975 (Fed. Cir. 2010).

ii. Findings of Fact

1. The level of ordinary skill in the art is a scientist responsible for drug formulation, such as a pharmaceutical chemist, physical chemist, medicinal chemist, or organic chemist, involved in the research and development of pharmaceutical compounds. The person of ordinary skill would have either: (1) a Ph.D., in a field related to pharmaceutical formulation and processing (such as pharmaceutical science, pharmacy, physical chemistry, organic chemistry, or pharmaceutics) and at least three years of experience in pharmaceutical compound development; or (2) a similar master's degree and at least five years experience in pharmaceutical compound development. Such an individual would also be familiar with or have access to the pertinent scientific literature.

2. The '820 patent is prior art.

3. The pH of the monosodium salt of ertapenem is about 5.5.

4. The '820 patent does not disclose the pH conditions required for the formation of the adduct.

5. The adduct would not necessarily form under the conditions described by the '820 patent.

6. The '820 patent does not anticipate the asserted claims of the '323 patent.

iii. Conclusions of Law

Defendant contends that the asserted claims of the '323 patent are inherently anticipated by the '820 patent. Specifically, Defendant contends that, although the '820 patent does not expressly disclose the carbamate adduct, the adduct will "'necessarily form' under the conditions taught by the '820 patent." (D.I. 211 at p. 6) (quoting Tr. 610:17-24). In other words, if one simply follows the steps of the '820 patent, the adduct will "just happen[]." (*Id.*) (quoting Tr. 884:18-885:6). I find otherwise. The '820 patent does not teach the key pH conditions for the formation of the adduct. Thus, while it is possible that the teachings of the '820 patent would result in the formation of the adduct, Defendant has not shown that the adduct will necessarily result.

The '323 patent states that the adduct does not form outside the pH range of "about 6.0 to about 9.0." (PTX 1 at 2:16-17). The '820 patent does not explicitly disclose this pH range, or, indeed, any other pH range. (Tr. 609:2-16). Defendant argues that a person of ordinary skill in the art,[5] reading the '820 patent, would recognize that it describes mixing a "sufficient amount of alkali carbonate or bicarbonate with ertapenem and at appropriate pH," such that the adduct will form. (Tr. 618:5-18).[6]

Defendant's argument hinges on the assertion that a person of skill in the art, when formulating ertapenem in accordance with the teachings of the '820 patent, would seek to obtain

[5] The parties agree that a person of ordinary skill in the art is "a scientist responsible for drug formulation, such as a pharmaceutical chemist, physical chemist, medicinal chemist or organic chemist, involved in the research and development of pharmaceutical compounds." (D.I. 191, Ex. 1 at 5-6). The person of ordinary skill has either "a Ph.D., in a field related to pharmaceutical formulation and processing . . . and at least three years of experience in pharmaceutical compound development; or . . . a similar master's degree and at least five years experience in pharmaceutical compound development." (*Id.* at 6). "Such an individual would also be familiar with or have access to the pertinent scientific literature." (*Id.*).

[6] The '820 patent teaches that "an acidic compound of the present invention may be dry blended with an alkali metal carbonate or bicarbonate." (DTX 19 at 7:13-15).

a pH in the 6.0 to 9.0 range described in the '323 patent. In support of its anticipation defense, Defendant relies on its expert, Dr. Timko. Dr. Timko begins his analysis by noting that the '820 patent teaches that ertapenem could be mixed with alkali carbonate or bicarbonate. (DTX 19 at 7:10-14; Tr. 601:2-13). Dr. Timko opines that the "purpose" of this mixture "would be to obtain approximately a seven pH."[7] (Tr. 606:13-20). This pH would be ideal, Dr. Timko contends, because it "would get a suitably stable dosage form." (Tr. 606:13-20; *see also* Tr. 609:9-16, 610:6-16). Additionally, Dr. Timko notes that the '820 patent also explains that "[a] preferred pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection." (DTX 19 at 7:40-43; Tr. 602:13-21). Dr. Timko contends this is important because intravenous injection at a pH other than neutral would be painful. (Tr. 608:5-14). Thus, Defendant maintains that a skilled artisan, reading the '820 patent, would seek "to obtain a suitable, appropriate intravenous, intramuscular, subcutaneous formulation . . . [by] mix[ing] sufficient bicarbonate or carbonate with the drug to a neutral pH to obtain a suitable product." (Tr. 610:6-16).

Dr. Timko's conclusion—that a person of ordinary skill would raise pH to optimize stability—finds little support in the evidence introduced at trial. Dr. Timko, rather than

[7] Ertapenem is polyionizable. (Tr. 781:9-24). There are four different ionic forms of it: the EH3 plus form (also, "fully protonated"), the "EH2 plus-minus" form, (also, "zwitterion"), the "EH minus" form (also, "monoanion" or "monosodium salt"), and the "dianion" form (also, "basic"). (Tr. 751:18-752:19, 801:15-804:6). In each of the first three forms, all of which are acidic, the pyrollidine group is fully charged. (Tr. 803:1-8, 808:18-809:1). When the pyrollidine group is charged, ertapenem cannot undergo polymerization, and it cannot react with a carbon dioxide source to form the adduct. (Tr. 803:9-11). Thus, only the dianion form can undergo polymerization or form the adduct. (Tr. 803:19-804:1, 806:19-807:5). At very low pH levels, ertapenem would likely exist only in the EH3 plus form, its most acidic form. (Tr. 801:22-802:8). As pH increases, ertapenem will exist in both the fully protonated and zwitterion form. (Tr. 802:11-16). As pH continues to increase, the fully protonated form will begin to disappear, and the monoanion form will begin to appear. (Tr. 802:18-23). The pH of the monosodium salt of ertapenem, the form upon which most of Plaintiff's anticipation theory is based, is about 5.5. (Tr. 425:18-24, 870:7-10, 886:20-23). When the pH is raised to about 6, the dianion form begins to appear. (Tr. 805:16-22).

explaining why an ordinary-skilled artisan would choose a neutral pH in a formulation, or how the '820 patent teaches that, relies on vague assertions. "[M]y education, my experience basically tell me that, you know, this is where you would want to be if you are going to be formulating the drug . . . . – you would want to optimize the stability, and you would want to optimize the pH." (Tr. 609:9-16; *see also* Tr. 606:13-20, 608:15-609:7).

Plaintiff's expert, Dr. Stella, provides several reasons why a person of ordinary skill in the art, reading the '820 patent, would not have formulated ertapenem at a neutral pH. Rather, Dr. Stella opines, a person of ordinary skill would have at least three good reasons to formulate ertapenem at a pH below 6.0. First, most hydrolytically unstable drugs, such as beta-lactams,[8] experience "maximum stability in the pH range of about 3.5 to 5." (Tr. 771:1-3, 797:21-798:1). Second, in the cases of thienamycin and ampicillin, two other beta-lactams, polymerization reaches optimal levels around pH values of 7 to 7.5. (Tr. 769:9-770:21). Thus, at neutral pH, a person of ordinary skill in the art would expect ertapenem to undergo polymerization, which would destroy the formulation. (Tr. 798:2-9). Third, meropenem, a structurally similar compound,[9] is most stable in solution at a pH between 5 and 6. (Tr. 786:11-787:10; PTX 409).[10]

Accordingly, a person of ordinary skill in the art would not necessarily choose a neutral pH as the target when seeking to achieve a stable pharmaceutical formulation of ertapenem. The '820 patent simply does not teach a target pH range of 6.0 to 9.0. Defendant's attempt to fill in that missing limitation with the knowledge of a person of ordinary skill is insufficient. The

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[8] While all beta-lactams are hydrolytically unstable (Tr. 773:11-14), Dr. Stella opined that carbapenems were "more unstable than both the pencillins and cephalosporins, which were two types of precursor beta-lactams, more popular at the time." (Tr. 765:4-9).

[9] The parties agree that meropenem is, at least in some respects, structurally analogous to ertapenem. (Tr. 90:24-91:14, 909:16-23).

[10] Specifically, in the presence of nucleophilic buffers, the pH of maximum stability was 5 to 5.5, while in the presence of non-nucleophilic buffers, the pH of maximum stability was around 6. (Tr. 786:11-787:10).

evidence shows that a person of ordinary skill in the art would not necessarily target the pH range required to form the adduct.

To illustrate this point, Dr. Stella provided three scenarios where formulating the acidic forms of ertapenem, according to the teachings of the '820 patent, would not form the adduct. In Scenario 1, Dr. Stella describes blending the "EH3 plus" form of ertapenem with sodium bicarbonate in a one to one mole ratio. (Tr. 820:1-11). The resulting solution would have a pH about 4, which is within the range of maximum stability for hydrolytically unstable drugs like ertapenem. (Tr. 820:17-20). Because the pH in such a scenario would be below 6, the adduct would not form. (Tr. 820:12-16). In Scenario 2, Dr. Stella describes blending the zwitterion form of ertapenem with sodium bicarbonate in a one to one mole ratio. (Tr. 822:2-12). The resulting formulation would have a pH of about 5 to 5.5. (Tr. 822:4-12). As in Scenario 1, this is within the pH range of maximum stability for most hydrolytically unstable drugs. (Tr. 822:23-823:1). Since the pH is below 6, the adduct would not form. (Tr. 822:13-17). In Scenario 3, Dr. Stella describes blending the monoanion form of ertapenem with 10 mg or 15 mg of sodium bicarbonate per gram of ertapenem. (Tr. 824:6-18, 825:24-826:11). Once reconstituted in solution, the resulting formulation would have a pH of about 5.7. (Tr. 824:19-825:1). Since the pH would again be too low—and not enough ertapenem would exist in the dianion form—the adduct would not form in any detectable amount. (Tr. 824:22-825:8, 825:16-23).

Dr. Stella opined that all three scenarios were consistent with the '820 patent. (Tr. 820:4-16, 822:7-12, 825:24-826:11). Additionally, the formulations described in the scenarios would be suitable for administration to a patient. (Tr. 661:1-11, 821:17-21, 823:12-15, 827:5-11).

Defendant insists that these are extreme, "cherry-picked" scenarios, which are inconsistent with the teachings of the '820 patent. (D.I. 211 at pp. 7-8). Beyond the conclusory

testimony of Dr. Timko, Defendants have not provided any evidentiary basis upon which to conclude that these scenarios are inconsistent with the teachings of the '820 patent. In fact, Dr. Timko admitted that, while these are not the only possible scenarios, a skilled formulator could "possibly select th[e]se scenarios." (Tr. 668:4-670:7). "The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *MEHL/Biophile*, 192 F.3d at 1365 (emphasis in original) (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)). "The disclosure [must be] sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function." *Id.* (quoting *In re Oelrich*, 666 F.2d at 581). Since the teachings of the '820 patent may or may not result in the formation of the adduct, there can be no inherent anticipation.

I conclude that Defendant has failed to show by clear and convincing evidence that the claimed invention is anticipated by the '820 patent.

B. Obviousness

i. Legal Standard

A patent claim is invalid as obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406-07 (2007). The determination of obviousness is a question of law with underlying factual findings. *See Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1360 (Fed. Cir. 2012). "The underlying factual inquiries include (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) any relevant secondary considerations . . . ." *Western Union Co. v. MoneyGram*

Payment Sys., Inc., 626 F.3d 1361, 1370 (Fed. Cir. 2010) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1078-79 (Fed. Cir. 2012). Relevant secondary considerations include commercial success, long-felt but unsolved needs, failure of others, praise, unexpected results, and copying, among others. *Graham*, 383 U.S. at 17-18; *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 662-63 (Fed. Cir. 2000); *Tex. Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993).

A party asserting that a patent is invalid as obvious must "show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). That "expectation of success need only be reasonable, not absolute." *Id.* at 1364. "Whether an ordinarily skilled artisan would have reasonably expected success . . . . is measured as of the date of the invention[] . . . ." *Amgen Inc. v. F. Hoffman-La Roche Ltd*, 580 F.3d 1340, 1362 (Fed. Cir. 2009).

ii. Findings of Fact

1. The level of ordinary skill in the art is a scientist responsible for drug formulation, such as a pharmaceutical chemist, physical chemist, medicinal chemist, or organic chemist, involved in the research and development of pharmaceutical compounds. The person of ordinary skill would have either: (1) a Ph.D., in a field related to pharmaceutical formulation and

processing (such as pharmaceutical science, pharmacy, physical chemistry, organic chemistry, or pharmaceutics) and at least three years of experience in pharmaceutical compound development; or (2) a similar master's degree and at least five years experience in pharmaceutical compound development. Such an individual would also be familiar with or have access to the pertinent scientific literature.

2. The '820 patent, Smith I, the label for Primaxin, Takeuchi III, and Remington's are prior art.

3. No prior art reference recites the formation of a carbamate adduct causing stabilization of a drug product.

4. The claimed invention was commercially successful.

5. Defendant copied the asserted claims of the '323 patent.

6. No others tried and failed to create a stable formulation of ertapenem.

7. The results described in the '323 patent were unexpected.

8. There was not a long-felt need for a stable formulation of ertapenem.

9. A person of ordinary skill would not have had a reasonable expectation of success in stabilizing ertapenem.

10. The asserted claims of the '323 patent would not have been obvious to one of ordinary skill in the art.

iii. Conclusions of Law

a. Scope and Content of Prior Art

To show that the '323 patent would have been obvious to one of ordinary skill in the art, Defendant relies on five prior art references: the '820 patent, the Smith I paper, the label for

Primaxin,[11] the Takeuchi III paper, and the Remington's textbook. Smith I, Primaxin, and Takeuchi III all relate to other carbapenems, specifically meropenem and imipenem. The '820 patent, as discussed above, relates to ertapenem.

Smith I, a paper published in August 1980, discusses the stability of imipenem. (DTX 304; Tr. 910:8-11). Smith I teaches that the carboxylic acid groups in imipenem contribute to its degradation. (Tr. 858:5-18, 861:1-17). Smith also teaches that, at 20° C, imipenem is most stable between a pH of 6 and 7. (Tr. 910:12-14).

The label for Primaxin shows that imipenem was buffered with sodium bicarbonate "to provide solutions in the pH range of 6.5 to 8.5." (DTX 309 at p. 0007).[12] Further, the label states that "[t]here is no significant change in pH when solutions are prepared and used as directed." (*Id.*).

Takeuchi III, a paper published in April 1995, describes the stability and degradation of meropenem in aqueous solution. (DTX 303). Meropenem, like ertapenem, forms dimers at its pyrollidine nitrogen. (Tr. 900:19-901:14, 902:6-16). Such dimerization contributes to meropenem's degradation. (*Id.*). Takeuchi III also taught that meropenem was most stable in solution at a pH between 5 and 6. (Tr. 786:11-787:10, 788:17-22; DTX 303).

Remington's, a textbook published in 1985, teaches that adjusting pH may help optimize stability. (PTX 425 at p. 257). Remington's also acknowledges that "ideal conditions for maximum stability may be unacceptable from the viewpoint of pharmaceutically acceptable

[11] Primaxin is Merck's brand name for its imipenem/cilastatin product.

[12] Plaintiff argues that this reference should not be considered, because it was published after the '323 patent's May 1996 priority date. (Tr. 684:17-685:4, 700:13-702:3). The label contains many dates, and I am not certain which information may have been reflected in the label which predates the '323 patent. Since I conclude that the label, in conjunction with Defendant's other references, does not render the claimed invention obvious, I will assume it is valid prior art for the obviousness analysis.

formulation or therapeutic efficacy, and it may be necessary to prepare a formulation with conditions less than optimum for stability of the drug." (*Id.*).

Plaintiff relies on Pratt, Archer, Yamana, Kovach, and the Takeuchi papers (I, II, and III) to show that the prior art taught away from the claimed invention. In Pratt, a beta-lactam molecule "reacts with . . . carbon dioxide to form a carbamate, but then the carbamate causes a rearrangement of the molecule." (Tr. 834:15-19; PTX 414). Thus, Pratt teaches the formation of the carbamate fundamentally changes the molecule. (Tr. 834:19-22). Similarly, Archer describes how the formation of a carbamate causes a rearrangement of a beta-lactam molecule, and thus "actually [leads] to degradation rather than stabilization." (Tr. 835:12-15, 836:8-11; PTX 413). Kovach, a paper published in 1975, also describes the formation of a carbamate. (Tr. Tr. 837:2-8; PTX 482). Kovach teaches that acetaminophen reacts with carbonate buffers to form a carbamate, which causes degradation. (Tr. 836-19:837:19).

Yamana, a paper published in 1977, states that a carbonate buffer, which reacted with the beta-lactam ring of a drug, was "the second most catalytic" of the buffers investigated. (Tr. 794:13-795:7; PTX 449). In other words, Yamana shows that carbonate, as a catalytic buffer, may cause degradation. (Tr. 828:2-14).

Takeuchi I and II teach that a dry blend of meropenem and sodium carbonate is stable. (Tr. 784:10-785:18; PTX 411; PTX 410). Those papers also teach, however, that when that dry blend is dissolved and then freeze-dried, the resulting product is extremely unstable. (Tr. 784:18-785:1, 786:3-7).

b. Comparison of the Prior Art and the Claimed Subject Matter

Defendant contends that the '323 patent is invalid as obvious over the '820 patent in light of the prior art references related to meropenem and imipenem. Defendant argues that these

prior art references "pointed like a beacon toward formulating ertapenem at neutral pH," and that under such conditions, the adduct would necessarily form. (D.I. 211 at p. 8). While none of these references expressly disclose the adduct, Defendant argues that "inherency . . . suppl[ies] [the] missing claim limitation in [the] obviousness analysis." *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1194-95 (Fed. Cir. 2014). In other words, Defendant argues that the adduct is an "an inherent property" of an obvious formulation. *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012); *see also In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011).

Plaintiff's cited prior art references do not teach that ertapenem should be formulated at neutral pH—i.e., under the conditions necessary for the adduct to form. A person of ordinary skill in the art would not have "a reasonable expectation of success in doing so." *Pfizer*, 480 F.3d at 1361. Instead, a person of ordinary skill in the art, at the time of invention, would have been faced, at best, with an array of inconclusive and sometimes contradictory teachings.

Defendant contends that "Takeuchi [III] taught that meropenem was more stable under neutral conditions." (D.I. 211 at p. 10 (citing DTX 303 at p. 0002)). To the contrary, Takeuchi III taught away from the patented invention, teaching that meropenem was most stable at a pH of 5 or 6. (Tr. 787:3-10, 788:17-22).[13] Takeuchi III also teaches that meropenem undergoes dimerization at around physiological pH.[14] (Tr. 798:2-9). Thus, to the extent one of skill in the art looked to the meropenem prior art for guidance, that person would expect that ertapenem would probably undergo that same reaction at around physiological pH. (*Id.*).

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[13] Defendant relies on the statement in Takeuchi III that meropenem "is relatively more unstable under acidic and alkaline conditions than under neutral condition[s], which is consistent with other β-lactam compounds." (DTX 303 at p. 0002). The data underlying this conclusion, as illustrated in Table 1, indicates that while this is generally true as a trend, the actual levels of maximum stability for meropenem are between 5 and 6. (*Id.*; *see also* Tr. 787:3-10, 788:17-22). This range is below the pH levels the '323 patent discloses as necessary for adduct formation.

[14] Physiological pH is about 7.4, though the parties use the term broadly to refer to pH values around 7. (Tr. 767:12-14, 775:9-15, 876:9-18).

Defendant argues that the prior art related to imipenem teaches formulating ertapenem at neutral pH. Defendant relies on Smith I, which generally teaches that imipenem is most stable between a pH of 6 and 7. (DTX 304 at pp. 0001-0002; Tr. 910:12-17). Defendant argues that Smith I also teaches that imipenem is unstable at low pH, and therefore, that a skilled artisan would expect ertapenem to be unstable at low pH. (D.I. 211 at pp. 9-10 (citing Tr. 861:1-17)). In support, Defendant cites to the testimony of Plaintiff's expert, Dr. Stella, arguing that he conceded this point. While Dr. Stella testified that Smith I and the '820 patent teach a skilled artisan that the carboxylic acid groups in ertapenem may contribute to instability, he did not testify that this had anything to do with low pH. (Tr. 861:1-17). Defendant also cites to the label for Primaxin as confirming to one of skill in the art that imipenem is most stable at a pH range of 6.5 to 8.5. (DTX 309 at p. 0007). Additionally, Defendant notes that the label discloses that the pH does not change during intravenous administration. (*Id.*). According to Defendant, this corroborates Remington's, which teaches that, "to be most suitable for injection, [a] solution should be about physiological[] pH." (D.I. 211 at p. 10). Altogether, according to Defendant, these references teach that, to achieve a stable drug product, imipenem should be formulated at a pH around neutral.

While the teachings related to imipenem may be instructive to one of ordinary skill in the art, there are important structural differences between imipenem and ertapenem, of which a person of ordinary skill would be aware. For instance, while imipenem may be isolated in crystalline form, the polyionizable character of ertapenem created difficulties in isolating a stable solid form. (Tr. 781:9-24). This led to the requirement that ertapenem be kept at -20° C in a freezer. (Tr. 781:17-782:2). Additionally, while imipenem is most stable at a pH between 6 and 7, that stability is not attributable to the formation of an adduct. (Tr. 779:6-15). In fact,

imipenem cannot form an adduct at all, since it has no pyrollidine nitrogen. (Tr. 779:6-781:5). Because of these differences, a skilled artisan would not reasonably expect that what had worked with imipenem would also work with ertapenem.

As discussed in the analysis of anticipation, the '820 patent does not mention any pH levels. As Dr. Stella's hypothetical scenarios demonstrate, the '820 patent does not guide a person of ordinary skill in the art toward formulating ertapenem at neutral pH.

Plaintiff argues that several prior art references taught away from the claimed invention. As illustrated in Pratt, Archer, and Kovach, the prior art taught that carbamate formation generally resulted in degradation. (Tr. 831:15-22). No prior art reference disclosed a carbamate adduct stabilizing a drug by preventing polymerization. (Tr. 829:22-830:8). Thus, a person of ordinary skill in the art would not have a reasonable expectation that the formation of a carbamate adduct would succeed in stabilizing ertapenem.

Therefore, the prior art does not teach an ordinary-skilled artisan to combine ertapenem with the requisite amount of bicarbonate/carbonate at a neutral pH, such that the adduct will form.

c. Secondary Considerations

"[S]econdary considerations, when present, must be considered in determining obviousness." *Ruiz*, 234 F.3d 654, 667; *see also Cyclobenzaprine*, 676 F.3d at 1076 ("[E]vidence on these secondary considerations is to be taken into account *always*, not just when the decisionmaker remains in doubt after reviewing the art." (internal quotation marks omitted) (quoting *Cable Elec. Prods. v. Genmark, Inc.*, 770 F.2d 1015, 1026 (Fed. Cir. 1985))). Here, Plaintiff has presented evidence of commercial success, copying, failure of others, unexpected results, and long-felt need.

1. Commercial Success

Both parties introduced expert testimony on commercial success. Defendant concedes that Plaintiff's Invanz product embodies the '323 patent. (D.I. 203 ¶ 3). Invanz generated $3.25 billion of sales worldwide and $1.8 billion of sales in the United States from 2002 to 2014. (Tr. 1012:20-1013:10; PTX 25; PTX 26). Invanz's sales and market share continually increased over that time period. (Tr. 1014:14-1015:11, 1016:12-1017:18, 1018:3-1019:8; PTX 25; PTX 27; PTX 28). Plaintiff's expert, Dr. Vellturo, opined that this growth was notable, given that several major antibiotics became available as generics during that period. (Tr. 1015:12-1016:11). In considering this evidence, Dr. Vellturo opined that Invanz has been a commercial success. (Tr. 1019:9-14).

Defendant's expert, Dr. Addanki, did not dispute that Invanz has been a commercial success, and instead focused his opinion on the nexus between Invanz's success and the '323 patent. (Tr. 710:12-24). "Evidence of commercial success . . . is only significant if there is a nexus between the claimed invention and the commercial success." *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011) (omission in original) (quoting *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006)). To show a nexus, a patentee must establish "that the sales were a direct result of the unique characteristics of the claimed invention." *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996); *see also J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997) (commercial success "must be due to the merits of the claimed invention beyond what was readily available in the prior art"). Dr. Addanki stated that Plaintiff's marketing materials focused on Invanz's clinical profile and once-daily dosing. (Tr. 713:20-715:1). Plaintiff's marketing materials did not mention the adduct, the manufacturing process, or the stabilized form. (*Id.*). This, according to Dr. Addanki, suggests

that the commercial success of Invanz is attributable to ertapenem itself, part of the prior art, rather than the stabilized form claimed in the '323 patent.

In response, Dr. Vellturo opined that, absent the '323 patent's stable formulation, and the '150 patent's manufacturing process, there would have been no product to market. (Tr 1021:2-1022:11). Defendant argues that this ignores several possible alternative methods for formulating a stable ertapenem product. For instance, Dr. Timko opined that ertapenem could have been developed as a "refrigerated product." (Tr. 644:18-645:21). Dr. Timko also referenced U.S. Patent No. 8,183,233 ("the '233 patent"), which discloses a method of stabilizing carbapenems by combining the carbapenem with water and a cyclodextrin, freezing that product, and later reconstituting it. (DTX 378; Tr. 645:22-647:7). The '233 patent explicitly mentions ertapenem as a "suitable pharmaceutical agent[] useful in embodiments of the present disclosure." (DTX 378 at 3:55-63). While this patent was issued in 2012, Dr. Timko opined that the technology described in the '233 patent would have been available in 1996. (Tr. 646:16-19).

I conclude that the commercial success of Invanz is sufficiently tied to the stable formulation described in the '323 patent. A company called Zeneca discovered the ertapenem compound. (Tr. 54:5-7).[15] In 1993, Zeneca granted Plaintiff an exclusive license to ertapenem. (Tr. 91:20-93:15, 718:23-719:8, 1036:1-16). According to Dr. Williams,[16] "Zeneca recognized that the development of a commercial process and a commercial formulation would be very difficult, and Merck had expertise in the development of carbapenems." (Tr. 54:8-55:13). Prior

[15] On October 4, 1993, Zeneca filed a U.S. patent application on ertapenem, and on December 26, 1995, the '820 patent issued. (DTX 19).

[16] Dr. Williams, a Merck employee, is a named inventor on the '323 patent. In December 1993, he, along with other Merck employees, met with the Zeneca employees who were responsible for the discovery of ertapenem. (Tr. 54:8-22).

to licensing ertapenem to Plaintiff, Zeneca determined that ertapenem was an unstable compound that required storage at -20° C. (Tr. 55:20-56:8). In particular, ertapenem was extremely unstable in solution,[17] such that "it under[went] decomposition . . . far too rapidly for administration in a hospital setting." (Tr. 59:13-60:10; *see also* Tr. 55:22-56:1). At the time Zeneca licensed ertapenem to Plaintiff, "a commercially viable formulation was not in place." (Tr. 56:9-58:12). The '323 patent solved this problem, and enabled Plaintiff to market a stable product. Therefore, the commercial success of Invanz was a result of the claimed invention.

The weight of the commercial success evidence is, however, discounted by the blocking effect of the '820 patent. Since ertapenem was claimed by the '820 patent, no entity aside from Zeneca, the original patentee, or Plaintiff, the exclusive licensee, had any incentive to develop a formulation for ertapenenem. (Tr. 718:23-719:8).[18] *See Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) ("Because market entry by others was precluded [due to patent protection and statutory exclusivity], the inference of non-obviousness . . . from evidence of commercial success . . . is weak."). Since the '820 patent blocked anyone other than Zeneca and Plaintiff from commercially exploiting ertapenem, no other industry players and the many persons of skill in the art employed by them had any incentive to develop alternative formulations for ertapenem. (Tr. 719:9-23). Therefore, while the stable formulation claimed by the '323 patent was commercially successful, the inference of non-obviousness from that fact is weak.

[17] Ertapenem must be in solution in order to be administered intravenously. (Tr. 59:24-60:10).
[18] Zeneca granted Plaintiff an exclusive license to the '820 patent, which covers the ertapenem compound. (Tr. 91:20-93:15).

2. Copying

"[C]opying by a competitor may be a relevant consideration in the secondary factor analysis." *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004). "[C]opying requires the replication of a specific product," which may be shown "through internal documents, direct evidence . . . or access to, and substantial similarity to, the patented product . . ." *Id.* (citations omitted). In the course of developing its generic product, Defendant considered "[u]sing different stabilizers other than carbon dioxide source (preferably Sodium chloride and/or Phosphate buffer)." (PTX 62 at p. 12). During development, Defendant tried at least five formulations that, according to Plaintiff, "would have avoided both the '323 and '150 patents because they used stabilizers that were not carbon dioxide sources." (D.I. 216 at p. 18). Instead, Defendant ultimately followed its "Primary Strategy," which was to use "[l]yophilization to obtain a stable product (reversible carbon dioxide adduct) using the process as per U.S. Patent 6486150B2," *i.e.*, the '150 patent. (PTX 62 at p. 12). This is evidence of copying. Defendant argues that copying is "not compelling evidence of nonobviousness" in a Hatch-Waxman case, since a generic drug manufacturer is required to copy the approved drug. *See Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 923 F. Supp. 2d 602, 676 (D. Del. 2013), *aff'd*, 752 F.3d 967 (Fed. Cir. 2014). Defendant is correct that 21 U.S.C. § 355(j)(2)(A) requires a generic to copy the active pharmaceutical ingredient of the reference drug, and to establish bioequivalency. The generic is not, however, required to copy inactive ingredients or the methods used in a manufacturing process. *Dey, L.P. v. Teva Parenteral Meds., Inc.*, 6 F. Supp. 3d 651, 681 (N.D.W. Va. 2014). Defendant's decision to copy Plaintiff's formulation and process "is an indicium of nonobviousness." *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 679 (Fed. Cir. 1988).

3. Failure of Others

Plaintiff argues that because Zeneca licensed ertapenem to Plaintiff, it must have failed to make its own stable formulation, thereby showing the failure of others. (D.I. 216 at pp. 18-19). Specifically, Dr. Williams and Dr. Vellturo infer that, because Zeneca licensed ertapenem to Plaintiff, it could not find a way to create a stable formulation of ertapenem. (Tr. 58:6-12, 105:208, 1023:15-16). This is far too speculative. There are many reasons why a company might not choose to undertake the process of taking an active pharmaceutical ingredient and developing a final formulated product. (Tr. 721:2-722:12). Plaintiff has not advanced evidence suggesting that anyone tried, and failed, to formulate stable ertapenem.

4. Unexpected Results

Plaintiff maintains that the formation of the adduct, with its associated stabilizing effect, constitutes an unexpected result. Dr. Williams, one of the inventors, testified that the stabilizing effect of adding bicarbonate was "a very surprising result," as he and the other inventors "had no reason to expect that bicarbonate would suppress the [formation] of dimers in solutions of ertapenem." (Tr. 66:8-21). Dr. Kaufman, another inventor, stated that he and the other inventors believed that sodium bicarbonate would function as an inert buffer. (Tr. 302:4-23). Defendant argues that the prior art reveals that carbamate adduct formation in solutions containing amines and carbon dioxide was well known. (D.I. 211 at p. 14 (citing Tr. 102:23-103:13)). Dr. Williams acknowledged this fact. (Tr. 102:23-103:13). Defendant also notes that carbamate adducts were known to form with other pharmaceutical compounds, such as penicillin. (Tr. 103:18-104:7, 650:11-652:12). Even assuming that the formation of the adduct was expected, the stabilizing effect of the adduct was unexpected. As explained earlier, adduct formation was known to cause degradation in prior art products, rather than an increase in stability. (*See, e.g.*,

Tr. 792:10-793:12). Thus, "[t]he unexpected properties of the claimed formulation, even if inherent in that formulation, differ in kind from the prior art, thereby supporting a conclusion of nonobviousness." *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1307 (Fed. Cir. 2015); *see also In re Spormann*, 363 F.2d 444, 448 (C.C.P.A. 1966) ("That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown."). In other words, "the previously unknown and unexpected properties of a new and nonobvious formulation constitute additional, objective evidence of nonobviousness." *Allergan*, 796 F.3d at 1307 (emphasis omitted).

5. Long-Felt Need

Plaintiff argues that Invanz satisfied a long-felt need. Plaintiff's expert, Dr. Solomkin, testified that, although existing carbapenems fulfilled certain needs, they required frequent infusions and had "too broad a spectrum." (Tr. 995:23-996:11). Dr. Stella testified that it would take "a high degree of creativity" to come up with an alternative formulation for ertapenem, but acknowledged that it was possible. (Tr. 850:7-18). Defendant contends that meropenem is very similar to ertapenem and satisfied whatever needs ertapenem fulfilled. (D.I. 211 at p. 14). Dr. Solomkin agreed that other carbapenems had similar antibiotic efficacy. (Tr. 992:18-22). Plaintiff argues that since ertapenem is not active against Pseudomonas bacteria, while meropenem is (Tr. 992:18-994:5), there is a long-felt need for ertapenem. I do not follow that argument. Perhaps there is some advantage to having one carbapenem for Pseudomonas and another for community-acquired infections, but that does not strike me as constituting a long-felt need. Additionally, ertapenem requires only one intravenous infusion per day, while meropenem requires three. (Tr. 989:3-8). This reduces the complexity of care, by requiring less nursing and pharmacy time, and increases efficacy, by maximizing the amount of time that the

concentration of the antibiotic within the blood is above the minimum effective concentration level. (Tr. 989:11-990:4). There is also a small safety benefit because of the risk of "potentially contaminated infusions." (Tr. 989:17-21). On balance, I am not convinced that there was a long-felt need for ertapenem.

There is also the issue of nexus. The satisfaction of any long-felt need described by Plaintiff is attributable to ertapenem, not to the stable formulation described in the '323 patent. Therefore, there is no "nexus between the evidence and the merits of the claimed invention." *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995). Plaintiff again argues that ertapenem would not be commercially available but for the '323 patent, but has failed to advance sufficient evidence to support that conclusion. I think there is a difference between "commercial success" and "commercial availability." The stable formulation may be necessary for commercial success. I do not see it as necessary for commercial availability. A "refrigerated product" would not have been a commercial success, but there is no reason why, if there was a long-felt need, it could not have been made commercially available.

d. Conclusion

This case does not present a scenario "where a skilled artisan merely pursues 'known options' from a 'finite number of identified, predictable solutions.'" *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) (quoting *KSR*, 550 U.S. at 421). Rather, this is a situation "where a defendant [has] merely throw[n] metaphorical darts at a board filled with combinatorial prior art possibilities." *Id.* Where, as here, a researcher is confronted with numerous variables and possibilities, and lacks adequate guidance from the prior art, it cannot be said that a particular combination was accompanied by "a reasonable expectation of success." *Pfizer*, 480 F.3d at 1361. Defendant argues that the prior art taught a person of ordinary skill to formulate

ertapenem at neutral pH, and, in doing so, a person of ordinary skill would have had a reasonable expectation of stabilizing ertapenem. I cannot agree.

If, at the moment before invention, a voice whispered to the inventors, "Do you think it'll work?" the answer would most likely have been, "I don't know." This is, at least in part, because neither the inventors, nor anyone else, had any understanding of the adduct's ability to stabilize ertapenem. Relatedly, and more importantly, the prior art did not lead a person of ordinary skill in the art to the conditions described in the '323 patent as a solution. In other words, the prior art did not teach a skilled artisan to combine ertapenem with bicarbonate/carbonate at a neutral pH. Thus, this is not a case where the prior art's "express teachings render the claimed . . . formulation obvious, and the claimed [adduct] adds nothing of patentable consequence." *Kao*, 639 F.3d at 1070; *see also Kubin*, 561 F.3d at 1357. The adduct is not merely an inherent property of an obvious formulation. Accordingly, Defendant has failed to show that the adduct is "the natural result of the combination of elements explicitly disclosed by the prior art." *Par Pharm.*, 773 F.3d at 1196.

Having considered the framework for obviousness laid out in *Graham* and *KSR*, I conclude that Defendant has failed to show by clear and convincing evidence that the claimed invention would have been obvious to one of ordinary skill in the art.

C. Written Description

i. Legal Standard

Section 112 ¶ 1 "contains a written description requirement separate from enablement." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). "[T]he description must 'clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.'" *Id.* (alteration in original) (quoting *Vas-Cath Inc. v. Mahurkar*, 935

F.2d 1555, 1563 (Fed. Cir. 1991)). "[T]he test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.* "[T]he level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Id.* "Whether the description requirement is met is a question of fact . . . ." *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985).

ii. Findings of Fact

The level of ordinary skill in the art is a scientist responsible for drug formulation, such as a pharmaceutical chemist, physical chemist, medicinal chemist, or organic chemist, involved in the research and development of pharmaceutical compounds. The person of ordinary skill would have either: (1) a Ph.D., in a field related to pharmaceutical formulation and processing (such as pharmaceutical science, pharmacy, physical chemistry, organic chemistry, or pharmaceutics) and at least three years of experience in pharmaceutical compound development; or (2) a similar master's degree and at least five years experience in pharmaceutical compound development. Such an individual would also be familiar with or have access to the pertinent scientific literature.

iii. Conclusions of Law

The '323 patent teaches that the carbamate adduct cannot form outside the pH range of 6.0 to 9.0. Defendant contends that because method claims 4 through 6 lack any limitation pertaining to pH, the claims are not commensurate in scope with the disclosures in the specification. Put another way, Defendant argues that the claims, which contain no pH

limitation, are broader than what is described in the specification, and are therefore invalid for lack of written description.

Defendant specifically relies on *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473 (Fed. Cir. 1998). There, the applicant attempted to amend claims to capture subject matter not described in the specification. Specifically, the applicant "identifie[d] the console as the only possible location for the controls" on a reclining sectional sofa. *Id.* at 1479. The disclosure thus "limited [the claims] to sofas in which the recliner control [was] located on the console." *Id.* The applicant was therefore not entitled to claims where the recliner controls were not located on the console. *Id.* at 1479-80. In short, the Federal Circuit concluded that "claims may be no broader than the supporting disclosure, and therefore that a narrow disclosure will limit claim breadth." *Id.* at 1480; *see also Cooper Cameron Corp. v. Kvaerner Oilfield Prods.*, 291 F.3d 1317, 1323 (Fed. Cir. 2002) (stating that *Gentry Gallery* "applied and merely expounded upon the unremarkable proposition that a broad claim is invalid when the entirety of the specification clearly indicates that the invention is of a much narrower scope").

Defendant's reliance on *Gentry Gallery* is misplaced. The patentee was not required to include a pH limitation in the claims of the '323 patent. There is no "'essential element' test mandating an inquiry into what an inventor considers to be essential to his invention and requiring that the claims incorporate those elements." *Cooper Cameron*, 291 F.3d at 1323. The key question is instead whether the claims "overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Ariad*, 598 F.3d at 1353-54; *see also Cooper Cameron*, 291 F.3d at 1323. Here, since the adduct does not form outside the pH range of 6.0 to 9.0, the omission of pH from the claims has no effect on the scope of the claims. (Tr. 851:14-852:8; *see also* PTX 1 at 2:14-20; Tr. 53:6-22, 652:20-653:4). Therefore, claims 4

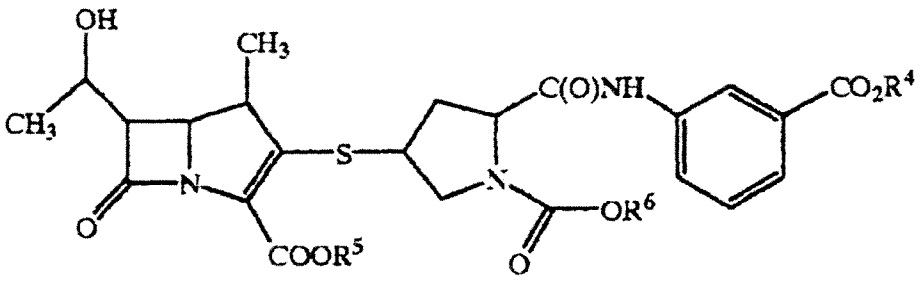
through 6 do not broaden the scope of the claims beyond the '323 patent's description. The '323 patent's disclosure therefore "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter." *Ariad*, 598 F.3d at 1351.

II. '150 PATENT

Independent claim 21 of the '150 patent reads:

A process for preparing a final formulation product of a compound of formula Ia,

Ia



or its pharmaceutically acceptable salt, or hydrates wherein, R^4, R^5, and R^6 are independently:

(a) hydrogen
(b) (C_1–C_6)-alkyl, or
(c) alkali-metal or alkali earth-metal wherein the alkali-metal or alkali earth-metal is sodium, potassium, lithium, cesium, rubidium, barium, calcium or magnesium;

comprising the steps of:

(1) charging a solution of carbon dioxide source having a pH range of about 6.0 to about 12.0 into a reaction vessel;
(2) adding an effective amount of a mole ratio of a base and an active ingredient into the reaction vessel containing the solution of carbon dioxide source to maintain pH at about 6.0 to about 9.0 and a temperature range of about -3° C to about 15° C.;
(3) lyophilizing the solution of Step (2) to yield the final formulation product of a compound of formula Ia with less than about 10% of moisture content.

(PTX 2 at 18:11-43). Dependent claims 22 through 34 contain numerous narrowing limitations, the substance of which is discussed in the validity analysis of those claims.

A. Claim Construction

"It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (internal quotation marks omitted). "'[T]here is no magic formula or catechism for conducting claim construction.' Instead, the court is free to attach the appropriate weight to appropriate sources 'in light of the statutes and policies that inform patent law.'" *SoftView LLC v. Apple Inc.*, 2013 WL 4758195, at *1 (D. Del. Sept. 4, 2013) (quoting *Phillips*, 415 F.3d at 1324). When construing patent claims, a court considers the literal language of the claim, the patent specification, and the prosecution history. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 977-80 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). Of these sources, "the specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315 (internal quotation marks and citations omitted).

"[T]he words of a claim are generally given their ordinary and customary meaning. . . . [Which is] the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* at 1312-13 (internal quotation marks and citations omitted). "[T]he ordinary meaning of a claim term is its meaning to [an] ordinary artisan after reading the entire patent." *Id.* at 1321 (internal quotation marks omitted). "In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *Id.* at 1314 (internal citations omitted).

When a court relies solely upon the intrinsic evidence—the patent claims, the specification, and the prosecution history—the court's construction is a matter of law. *See Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015). The court may also make factual findings based upon consideration of extrinsic evidence, which "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Phillips*, 415 F.3d at 1317-19 (internal quotation marks and citations omitted). Extrinsic evidence may assist the court in understanding the underlying technology, the meaning of terms to one skilled in the art, and how the invention works. *Id.* Extrinsic evidence, however, is less reliable and less useful in claim construction than the patent and its prosecution history. *Id.*

"A claim construction is persuasive, not because it follows a certain rule, but because it defines terms in the context of the whole patent." *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998). It follows that "a claim interpretation that would exclude the inventor's device is rarely the correct interpretation." *Osram GmbH v. Int'l Trade Comm'n*, 505 F.3d 1351, 1358 (Fed. Cir. 2007) (internal quotation marks and citation omitted).

The Court held a Markman hearing on July 30, 2015. (D.I. 137). At that time, the Court offered a preliminary construction of the term "the final formulation product of a compound of formula Ia." (*Id.* at 95-96). The Court determined that the term required that the process "achieve the stabilized form of carbon dioxide [or, carbamate] adduct in the final composition" by "'a high rate conversion' . . . from the carbapenem salt to the carbon dioxide adduct." (*Id.*). The parties now dispute what is meant by "a high rate conversion," as it relates to the final formulation product. Plaintiff contends a "'high rate conversion' is a rate that results in a mixture of ertapenem and the carbon dioxide adduct with the latter present in an amount

sufficient to stabilize the formulation and provide for a low level of degradants." (D.I. 210 at pp. 4-5). Put another way, "high rate conversion" is defined functionally as a conversion which provides "low by-product formation." Defendant, framing its argument in a slightly different way, argues that "the final formulation product of a compound of formula Ia" should be construed as "a lyophilized product resulting from about 80% conversion to the carbamate." (D.I. 217 at p. 6). In other words, Defendant argues that "a high rate conversion" is a conversion where 80% of the carbapenem salt is converted to the adduct.

The '150 patent does not explain what percentage of adduct, converted from the carbapenem salt, would constitute a "high rate conversion." (Tr. 187:24-188:4). To divine the meaning of the term, the parties focus on one passage from the specification, where the '150 patent explains that "[t]he present process provide[s] a high rate conversion from the alkali metal salt, such as monosodium salt of carbapenem[,] to the carbon dioxide adduct and the low by-product formation, such as dimers and open ring compounds." (PTX 2 at 9:13-17). Plaintiff argues that this means the "high rate conversion" describes the way in which the patent achieves its "low by-product formation" result. Defendant argues that the use of the word "and" in the "and the low by-product formation" phrase indicates that "[l]ow by-product formation is a feature that is separate from, and in addition to, high rate conversion to the adduct." (D.I. 217 at p. 7). In other words, Defendant argues that the '150 patent's specification describes two goals: (1) a high rate conversion, and (2) a process of minimizing degradation. (*Id.*; Tr. 416:5-417:15).

Read as a whole, the '150 patent's specification suggests that the proper construction is that the "high rate conversion" is the means of achieving low by-product formation. The specification includes four examples of the claimed invention. In each of these examples, the specification includes information about the total amounts of degradants, dimers, and open ring

compounds. (PTX 2 at 12:20-15:63 tbls. 2, 4, & 7; *see also* Tr. 188:15-24). The specification does not explain what percentage of carbapenem is converted into the adduct. Nor does the '150 patent mention any level of adduct which is required to achieve these low levels of degradants. (Tr. 187:15-23). Rather, a high rate conversion is simply a conversion wherein enough of the adduct was formed so that the resulting final formulation products were stable, with low levels of degradants. (Tr. 221:16-20). The focus of the invention is on minimizing degradants through a conversion, rather than maximizing the amount of salt which is converted. This reading finds further support elsewhere in the specification. In the Background of the Invention, the '150 patent notes that the prior art "fail[ed] to teach how to achieve the conversion of salt-containing carbapenem compound to a formulation exhibiting acceptable levels of degradates required for solid state and reconstitution stability for dosing to patients." (PTX 2 at 2:30-38). This confirms that the goal of the invention, and of the high rate conversion, was to minimize degradants.

In support of its construction, Defendant relies solely on the testimony of its expert, Dr. Murgatroyd. Without citing to any documents, Dr. Murgatroyd opines that a high rate conversion means an 80 percent yield. (Tr. 405:23-406:17, 440:22-441:1, 509:1-9). This figure finds little support in the patent's specification, the prosecution history, or the claims. (*See* Tr. 508:10-19, 510:9-16). Dependent claim 24, which depends from independent claim 21, claims a "mole ratio of carbon dioxide source to the active ingredient [of] about 0.5 to about 1.5." (PTX 2 at 18:52-56). As conceded by Dr. Muragtroyd, a 0.5 ratio of carbon dioxide source to active ingredient could not produce a yield higher than 50%. (Tr. 497:16-498:4). Thus, Defendant proposes a construction which excludes a dependent claim from the scope of the independent claim from which it depends. To put it another way, Defendant argues that the "final formulation product" claimed in claim 21 means at least an 80 percent yield. (Tr. 405:23-

406:13). Since dependent claim 24 contemplates a yield as low as 50%, Defendant's construction would exclude that dependent claim from the scope of the claim from which it depends. This construction should be avoided. *See, e.g.*, *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012) ("It is axiomatic that a dependent claim cannot be broader than the claim from which it depends"); *Intamin Ltd. v. Magnetar Techs., Corp.*, 483 F.3d 1328, 1335 (Fed. Cir. 2007) ("An independent claim impliedly embraces more subject matter than its narrower dependent claim.").

I therefore adopt Plaintiff's construction. A "high rate conversion" is construed as "a rate that results in a mixture of ertapenem and the carbamate adduct with the latter present in an amount sufficient to stabilize the formulation and provide for a low level of degradants."

B. Infringement

i. Legal Standard

"Under [35 U.S.C.] § 271(e)(2)(A), a court must determine whether, if the drug were approved based upon the ANDA, the manufacture, use, or sale of that drug would infringe the patent in the conventional sense." *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997). The application of a patent claim to an accused product is a fact-specific inquiry. *See Kustom Signals, Inc. v. Applied Concepts, Inc.*, 264 F.3d 1326, 1332 (Fed. Cir. 2001). Literal infringement is present only when each and every element set forth in the patent claims is found in the accused product.[19] *See Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575-76 (Fed. Cir. 1995). The patent owner has the burden of proving infringement by a preponderance of the evidence. *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 758 (Fed. Cir. 1984). Infringement can be shown by "any method of analysis that is probative of the fact of

[19] There are no assertions of infringement by the doctrine of equivalents.

infringement," and, in some cases, "circumstantial evidence may be sufficient." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009).

ii. Findings of Fact

Defendant's ANDA product contains amounts of the carbamate adduct sufficient to stabilize the formulation and provide for a low level of degradants.

iii. Conclusions of Law

Defendant agrees that every limitation of claims 21-34 is satisfied, other than the "final formulation product" limitation. (D.I. 203 ¶ 1). Thus, the only question is whether the adduct is "present in an amount sufficient to stabilize the formulation and provide for a low level of degradants." Defendant concedes that its product contains the adduct. (*Id.* ¶ 14). Both Plaintiff and Defendant "have used . . . processes . . . which resulted in cakes that had low enough levels of . . . degradants that they met specifications." (Tr. at 218:12-220:9, 512:16-514:13; *see also* PTX 479; PTX 550).

The amount of adduct in Defendant's product is sufficient to reduce dimer formation and provide a stable product.[20] Therefore, Defendant's product satisfies the "final formulation product" limitation. Defendant's ANDA product will thus be made by a process which literally infringes the asserted claims of the '150 patent.[21]

[20] To detect the amount of adduct in Defendant's lyophilized product, both parties rely on nitrogen-15 solid state nuclear magnetic resonance testing. The parties dispute which data, and which analysis, accurately reflects the level of adduct in Defendant's product. Properly construed, the "final formulation product" limitation does not require any quantification. Therefore, I need not and do not resolve these disputes.

[21] "To be sure, if at the end of the day, an act that would have been an infringement . . . pertains to a patent that is shown to be invalid, there is no patent to be infringed." *Commil USA, LLC v. Cisco Sys., Inc.*, 135 S. Ct. 1920, 1929 (2015). Since I ultimately conclude that the '150 patent is invalid as obvious, there is ultimately no infringement.

C. Obviousness

i. Findings of Fact

1. The level of ordinary skill in the art is either (1) a person with a Ph.D. in organic chemistry, medicinal chemistry, chemical engineering, or a related discipline, and two to five years of experience; or (2) a person with a lesser degree with additional work experience. Additionally, a person of ordinary skill in the art would understand the relevant chemical literature.

2. The '323 patent and Almarsson are prior art.

3. The '323 patent and Almarsson both teach that the formation of the adduct is dependent on pH, and that formation of the adduct requires a pH range of about 6.0 to about 9.0.

4. The '323 patent and Almarsson both teach that sodium hydroxide could be used to adjust pH.

5. The '323 patent and Almarsson both teach that the carbamate adduct could be produced using lyophilization.

6. A person of ordinary skill in the art would have known that temperature was a result-effective variable.

7. The optimization of the temperature range for the reaction would have been routine to one of ordinary skill in the art.

8. Plaintiff's product, which utilizes the claimed process, is a commercial success.

9. Defendant copied the manufacturing process recited in the asserted claims of the '150 patent.

10. There was not a long-felt need for the manufacturing process described in the asserted claims of the '150 patent.

11. The asserted claims of the '150 patent would have been obvious to a person having ordinary skill in the art.

ii. Conclusions of Law

Defendant contends that the '150 patent is invalid as obvious under two separate bases: (1) it is obvious over the '323 patent in light of the knowledge of a skilled artisan, and (2) it is obvious over the Almarsson patent application in light of the knowledge of a skilled artisan.

The parties have presented similar definitions for a person of ordinary skill in the art. For Defendant, Dr. Murgatroyd testified that a person of ordinary skill would have "a Ph.D. in a field related to pharmaceutical formulation and processing, and probably about three years experience in the field of the pharmaceutical industry, and with a Master's, probably five years experience." (Tr. 393:10-15). For Plaintiff, Dr. Stahly opined that a person of ordinary skill "would be someone with a Ph.D. degree in organic chemistry, maybe medicinal chemistry, chemical engineering, or related discipline, and in addition would need probably two to five years of experience." (Tr. 180:4-12). Dr. Stahly also stated that it was "possible someone could be skilled in the art without the Ph.D., but they would have needed additional work experience." (Tr. 180:13-18). In either case, Dr. Stahly testified that a person of ordinary skill "would [also] have to know how to utilize and understand the chemical literature." (Tr. 180:16-18). Dr. Murgatroyd stated that, even if the Court adopted Dr. Stahly's definition, his opinion would not change. (Tr. 393:24-394:5). I do not think the difference in definitions is material to the outcome. I adopt Dr. Stahly's definition.

a. Claim 21

As indicated above, claim 21 of the '150 patent discloses a manufacturing process for "preparing a final formulation product." The steps are:

(1) charging a solution of carbon dioxide source having a pH range of about 6.0 to about 12.0 into a reaction vessel;
(2) adding an effective amount of a mole ratio of a base and an active ingredient into the reaction vessel containing the solution of carbon dioxide source to maintain pH at about 6.0 to about 9.0 and a temperature range of about -3° C. to about 15° C.;
(3) lyophilizing the solution of Step (2) to yield the final formulation product of a compound of formula Ia with less than about 10% of moisture content.

(PTX 2 at 18:32-43).

1. '323 Patent

Defendant contends that claim 21 is obvious over the '323 patent in light of the knowledge of a skilled artisan. A skilled artisan, armed with the "recipe" taught by the '323 patent, Defendant argues, would have found claim 21 of the '150 patent obvious.

The '323 patent taught that ertapenem was unstable, and that stability was related to pH. (Tr. 395:12-396:1, 397:7-399:16). Specifically, the '323 patent taught that "stabilization occurred in the pH range from about 6 to 9." (Tr. 816:22-817:1, 431:24-432:11; PTX 1 at 2:14-20). This was a "sweet spot" because the solution would not suffer from destabilizing hydrolysis, and the formation of the carbamate would prevent the polymerization reaction. (Tr. 817:7-19).

The '323 patent also explained that "[o]ther compounds c[ould] be included to adjust the pH of the composition upon dilution or reconstitution." (PTX 1 at 3:15-18). The '323 patent provided several examples, including sodium hydroxide. (*Id.* at 3:17-18).

The '323 patent discloses that the carbamate adduct may be produced using "standard lyophilization techniques." (Tr. 957:12-20; PTX 1 at 3:38-40).

The steps recited in claim 21 are an obvious implementation of the '323 patent into a manufacturing process. Step (1) recites "charging a solution of carbon dioxide source having a pH range of about 6.0 to about 12.0 into a reaction vessel." (PTX 2 at 18:33-35). A skilled

artisan, seeking to follow the teachings of the '323 patent, would begin a manufacturing process by creating a solution of carbon dioxide source at a pH of 6 to 9. (Tr. 422:5-423:10). As explained by Dr. Murgatroyd, by first adjusting the pH of the carbon dioxide source, ertapenem—which is sensitive to pH—may be added directly to a solution that is at the preferred pH. (Tr. 424:13-425:11). This minimizes the amount of time that ertapenem spends in solution at unstable pH levels. (*Id.*).

Step (2) recites "adding an effective amount of a mole ratio of a base and an active ingredient into the reaction vessel containing the solution of carbon dioxide source to maintain pH at about 6.0 to about 9.0 and a temperature range of about -3° C. to about 15° C." (PTX 2 at 18:36-40). After creating a solution of a carbon dioxide source and water at stable pH, a skilled artisan would add the active ingredient. (Tr. 437:10-15). In doing so, a skilled artisan would seek to maintain the pH of ertapenem in solution at a pH between about 6 to about 9, since that is precisely what was taught by the '323 patent. (Tr. 431:24-432:11; PTX 1 at 2:14-20). The '323 patent explicitly notes that a base, such as sodium hydroxide, can be be used to adjust the pH of the composition. (PTX 1 at 3:15-18; Tr. 438:9-23). The '323 patent does not disclose the simultaneous addition of sodium hydroxide and ertapenem. A skilled artisan, however, would know that the monosodium salt of ertapenem sodium has a pH of about 5.5. (Tr. 425:18-24, 870:7-10, 886:20-23). Thus, to counteract the acidifying effect of the ertapenem salt—and thus keep the solution pH in the target range—a skilled artisan would simultaneously add a base, such as sodium hydroxide. (Tr. 423:11-22, 928:9-16).

Lower temperatures tend to slow most degradation reactions, while higher temperatures tend to accelerate degradation reactions. (Tr. 423:23-424:12). This is widely known to those of skill in the art. (Tr. 89:20-90:12, 423:23-424:12, 924:22-925:8). Since a person of ordinary skill

would know of ertapenem's tendency to degrade, that person would seek to chill the solution of ertapenem to a low temperature. (Tr. 438-24-439:11). Specifically, a person of ordinary skill in the art would attempt to cool the solution to reach the lowest possible temperature without freezing.[22] (*Id.*, Tr. 467:4-16; *see also* Tr. 439:5-11). Dr. Murgatroyd therefore opined that a person of ordinary skill in the art would have arrived at the claimed temperature range. (Tr. 467:2-21). "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (alteration in original) (quoting *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955));[23] *see also KSR*, 550 U.S. at 421 ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.").

Step (3) requires "lyophilizing the solution of Step (2) to yield the final formulation product of a compound of formula Ia with less than about 10% of moisture content." (PTX 2 at 18:41-43). The lyophilization process is important, as it removes the water from the composition, thereby stabilizing the remaining solid material. (Tr. 929:15-20; *see also* Tr. 426:5-20). Claim 21 does not specify any particular lyophilization conditions. (PTX 2 at 18:41-43; Tr. 977:6-11). Dr. Murgatroyd opined that a moisture content of 0.5 percent to 3.0 percent was common at the time of invention. (Tr. 427:16-430:5; *see* also DTX 359 at pp. 34-35).

[22] Since ertapenem causes a depression in the freezing point of water, an ertapenem solution maintained at a temperature slightly below 0° C would not freeze. (Tr. 467:11-16).

[23] "This rule is limited to cases in which the optimized variable is a 'result-effective variable.'" *Id.* (quoting *In re Antonie*, 559 F.2d 618, 620 (C.C.P.A. 1977)). In this case, there is little doubt that the results of temperature manipulation were recognized by those of skill in the art, as acknowledged by Drs. Williams, Murgatroyd, and Stahly. (Tr. 89:20-90:12, 423:23-424:12, 924:22-925:8).

Further, Dr. Muragtroyd testified that a skilled artisan would be able to achieve a moisture content below 10% with routine optimization. (Tr. 427:16-430:5).[24]

Properly construed, the "final formulation product" limitation requires adduct formation sufficient to stabilize the final formulation product. By Plaintiff's own admission, the '323 patent teaches compositions with adduct formation sufficient to stabilize the product, such that it is suitable for administration to patients by injection. (Tr. 878:10-879:6).

Plaintiff's expert, Dr. Stahly, opined that "the steps, the order of the steps, the details of how each step is carried out are not presented in [the '323] patent." (Tr. 942:7-18). I conclude that the order of the steps would have been obvious to a person of skill in the art. Dr. Stahly concedes that adding the active ingredient without the base present "would drive the pH down, and it would lead to protonation of pyrollidine amine, so that the adduct would not form, and it would also be in a region where hydrolysis would be faster." (Tr. 928:9-16). If, in order to adjust the pH of the solution, the base was added before the active ingredient, "that would drive the pH higher, and then when the active ingredient went in, . . . hydrolysis would be faster than desired." (Tr. 928:17-24). If all three ingredients were placed in solution at the same time, the resulting "uncontrolled situation" with "many competing reactions" would be expected to create "high levels of degradants." (Tr. 929:1-9). The '323 patent may not explicitly lay out the steps claimed in the '150 patent, but that is not what an obviousness inquiry requires. "A person of ordinary skill is also a person of ordinary creativity, not an automaton." *KSR*, 550 U.S. at 421. Indeed, "[i]n *KSR*, the Supreme Court criticized a rigid approach to determining obviousness based on the disclosures of individual prior-art references, with little recourse to the knowledge, creativity, and common sense that an ordinarily skilled artisan would have brought to bear when

[24] While lyophilization parameters are product-specific (Tr. 930:18-24), claim 21 does not specify any particular lyophilization conditions.

considering combinations or modifications." *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013); *see also KSR*, 550 U.S. at 418 ("The analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.").

Claim 21 is a general recitation of routine manufacturing steps which would have been obvious to one of ordinary skill in the art. A person of ordinary skill, seeking a manufacturing process for the compound disclosed in the '323 patent, would predictably arrive at the solution described in the '150 patent, and would reasonably expect that it would succeed. In other words, "the differences between [claim 21] and [the '323 patent] are such that claim 21 as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103. I conclude that Defendant has made a *prima facie* showing that claim 21 is obvious over the '323 patent.

2. Almarsson

Defendant contends that claim 21 is obvious over Almarsson in light of the knowledge of a skilled artisan. Almarsson is an international patent application filed by Plaintiff's employee Örn Almarsson. (DTX 294). Since Almarsson's disclosures are very similar to those of the '323 patent, Defendant's theory of obviousness is similar.

Like the '323 patent, Almarsson discloses the parameters required for the formation of the adduct: (1) a pH range of "about 6.0 to about 9.0," or preferably, "about 6.2 to about 8.5;" (2) using sodium carbonate or bicarbonate in the same ratios with the active ingredient; (3) adjusting the pH with a base, such as sodium hydroxide; and (4) lyophilizing "using standard lyophilization techniques." (DTX 294 at pp. 14-15, 22-23; *see also* PTX 1 at 2:14-20, 3:8-40).

Just as these disclosures rendered claim 21 obvious when taught by the '323 patent, they render claim 21 obvious here.

In addition to these disclosures, Almarsson includes data about the stability of ertapenem in solution. (DTX 294 at p. 31). Dr. Murgatroyd explained that the graph from Example 3 shows that ertapenem in solution at pH 7.5 and a temperature of 5° C, in the absence of carbonate, undergoes dimerization at a constant rate. (*Id.*; Tr. 448:16-449:21). The graph also shows that, under the same conditions, the presence of carbonate, a carbon dioxide source which results in the formation of the adduct, causes dimer formation to stop after an initial period. (DTX 294 at p. 31; Tr. 448:16-449:21). The "carbonate-buffered" formulation, under solid state conditions at 25° C, remained stable for "twelve or more weeks." (DTX 294 at p. 31). According to Dr. Murgatroyd, this additional data about temperature provides "a good indication . . . to keep the temperature low . . . [to] slow down degradant reactions." (Tr. 449:16-21). Further, the data on dimer formation shows that the bicarbonate, by forming the adduct, "protect[s] against dimer formation." (Tr. 449:10:15).

I therefore conclude that Defendant has made a *prima facie* showing that claim 21 is obvious over Almarsson.

b. Claims 22-34

Defendant argues that dependent claims 22 through 34 are obvious over both the '323 patent and Almarsson. "[E]ach claim must be considered as defining a separate invention." *Jones v. Hardy*, 727 F.2d 1524, 1528 (Fed. Cir. 1984). "Each claim . . . shall be presumed valid independently of the validity of the other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim." 35 U.S.C. § 282. This "independent evaluation is necessary because dependent claims necessarily add limitations to the

claims from which they depend . . . ." *Dana Corp. v. Am. Axle & Mfg., Inc.*, 279 F.3d 1372, 1376 (Fed. Cir. 2002).

The dependent claims add several narrowing limitations to steps (1) and (2). Claim 22 requires that the carbon dioxide source be selected from a particular list. (PTX 2 at 18:44-49). Claim 23 recites that the carbon dioxide source is sodium bicarbonate. (*Id.* at 18:50-51). Claims 24 and 25 recite specific mole ratios of the carbon dioxide source to an active ingredient: about 0.5 to about 1.5, and about 0.8 to about 1.2, respectively. (*Id.* at 18:52-61). Claim 26 and 27 narrow the pH range and temperature range recited in step (1) to a pH range of about 7.0 to about 9.0, and a temperature range of about -3° C to about 15° C. (*Id.* at 62-65). Claim 28 defines the active ingredient as ertapenem. (*Id.* at 18:66-19:11; Tr. 199:12-18, 460:2-7)). Claim 29 requires that the base be selected from a particular list. (PTX 2 at 19:12-20). Claim 30 narrows the base of step (2) to about 1N to about 3N of sodium hydroxide. (*Id.* at 19:21-22). Claims 31 and 32 recite specific mole ratios of the base to an active ingredient: about 0.7 to about 1.0, and about 0.8 to about 0.9, respectively. (*Id.* at 19:23-28). Claims 33 and 34 narrow the pH range and temperature range recited in step (2) to a pH range of about 7.0 to about 8.0, and a temperature range of about -1° C to about 5° C. (*Id.* at 19:19-20:2).

Dr. Murgatroyd opined that each of these claims would have been obvious in view of both the '323 patent and Almarsson. As to claims 22, 23, 24, and 25, the '323 patent and Almarsson disclose sodium bicarbonate as a carbon dioxide source in a one-to-one molar ratio with ertapenem. (Tr. 456:13-458:5). Claims 26 and 27 would have been obvious to one of ordinary skill for the same reasons the claimed pH and temperature ranges in step (2) of claim 21 were obvious. (Tr. 458:9-459:6). Since the '323 patent and Almarsson teach ertapenem as an active ingredient, claim 28 also would have been obvious. (Tr. 460:5-13). Dr. Murgatroyd

opined that claims 29 and 30 would have been obvious to one of skill in the art, as the '323 patent and Almarsson disclosed using sodium hydroxide to adjust pH. (Tr. 460:18-461:14). While Dr. Murgatroyd noted that claim 30's specific concentrations were not disclosed in either the '323 patent or Almarsson, he opined that the recited concentrations—a range of one to three normal—were commonly used by persons of ordinary skill, in order to minimize pockets of extreme pH. (Tr. 461:11-463:11). Dr. Murgatroyd opined that claims 31 and 32 would have been obvious, as an artisan of ordinary skill would, in practicing the '323 patent or Almarsson, "automatically" arive at the claimed mole ratios. (Tr. 463:10-465:7).[25] According to Dr. Murgatroyd, claim 33 would have been obvious, as the '323 patent and Almarsson teach a pH range of about 6 to about 9, and arriving at a narrower range would have been routine optimization to one of skill in the art. (Tr. 465:16-466:13). Similarly, the narrower temperature range claimed in claim 34 would have been obvious, through routine optimization, to an ordinary-skilled artisan seeking to minimize degradation. (Tr. 466:22-467:21).

While the validity of each claim rises or falls independently, Plaintiff did not provide any evidence in support of each dependent's claim validity. Rather, Plaintiff focused entirely on the validity of claim 21. Thus, Dr. Murgatroyd's invalidity testimony on the dependent claims' additional limitations was not disputed.

I conclude that Defendant has made a *prima facie* showing that claims 22-34 of the '150 patent are invalid as obvious.

[25] Dr. Murgatroyd explains that, as ertapenem is added to a solution with a pH of about between 6 and 9, the solution will become more acidic. (Tr. 464:1-8). Thus, to raise the pH, thereby cancelling out the effect of the ertapenem, one would add the appropriate amount of base. (Tr. 464:8-465:1). The "end result" of this "would be the correct mole ratio," as specified in claims 31 and 32. (Tr. 465:2-7).

c. Secondary Considerations

Plaintiff argues that all of the evidence of commercial success, copying, and long-felt need discussed in connection with the '323 patent also applies with respect to the '150 patent.

The discussion of commercial success, copying, and long-felt need, with respect to the formulation described in the '323 patent, applies with equal force to the manufacturing process claimed in the '150 patent. In summary, Plaintiff has not shown evidence of long-felt need, but has shown evidence of copying and commercial success.[26] While the copying and commercial success evidence supports the argument for non-obviousness, "secondary considerations of nonobviousness . . . simply cannot overcome a strong prima facie case of obviousness." *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010).

Having considered the framework for obviousness laid out in *Graham* and *KSR*, I conclude that claims 21-34 of the '150 patent would have been obvious to one of ordinary skill in the art.

D. Anticipation

i. Findings of Fact

1. The level of ordinary skill in the art is either (1) a person with a Ph.D. in organic chemistry, medicinal chemistry, chemical engineering, or a related discipline, and two to five years of experience; or (2) a person with a lesser degree with additional work experience. Additionally, a person of ordinary skill in the art would understand the relevant chemical literature.

2. The Tsinontides manuscript is prior art.

[26] I previously concluded that the '820 patent's effect as a blocking patent weakened the evidence of commercial success with respect to the stable formulation claimed in the '323 patent. I conclude the same with respect to the manufacturing process recited in the '150 patent.

3. The Tsinontides manuscript does not disclose charging a solution of carbon dioxide source, having a pH range of about 6.0 to about 12.0, into a reaction vessel.

4. The Tsinontides manuscript does not disclose adding an effective amount of a mole ratio of a base and an active ingredient into the reaction vessel containing the solution of a carbon dioxide source.

5. The Tsinontides manuscript does not anticipate the '150 patent.

ii. Conclusions of Law

Defendant argues that slide presentation authored by inventor Stelios Tsinontides ("the Tsinontides manuscript"), and presented at a conference in 1999, anticipates claims 21 through 29. The parties first dispute whether the Tsinontides manuscript qualifies as prior art. Since I conclude that the Tsinontides manuscript does not anticipate claims 21 through 29 of the '150 patent, I need not address the question of whether the manuscript qualifies as prior art. I will accept, for purposes of the anticipation analysis, that the Tsinontides manuscript is 35 U.S.C. § 102(b) prior art.

Defendant argues that, although the exact words of claim 21 do not appear in the manuscript, it discloses the substance of the claimed invention. (Tr. 477:3-24; D.I. 211 at p. 30). I disagree. The slides only generally describe the problems that the '150 patent sought to solve. For instance, slide 16 refers to the "[b]alancing [a]ct" of controlling dimerization and ring-opening hydrolysis. (PTX 269 at p. 16). In that slide, Dr. Tsinontides explains that "[m]anufactring [l]osses" may be "[m]inimize[d]" by forming the adduct with carbon dioxide from carbonate, adjusting pH with sodium hydroxide, and using a "[r]apid [c]ompounding [p]rocess at 5° C." (*Id.*). The slide also refers to three different lyophilized formulations: .84, 1.0, and 1.25 mole-equivalents of carbonate. (*Id.*). On slide 17, Dr. Tsinontides indicates that he

had achieved moisture contents of about 2%. (*Id.* at p. 17). Slide 22 refers to the same formulations described in slide 16. (*Id.* at p. 22). The chart on slide 22 shows experimental results which reflect the level of carbonate at the three different stages of initial charging, pre-lyophilization, and the final product. (*Id.*).

The slides do not describe the process recited in claims 21 through 29. While a "reference need not satisfy an *ipsissimis verbis* test," the reference "must disclose each and every element of the claimed invention," with those elements "'arranged or combined in the same way as in the claim.'" *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009) (quoting *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1370 (Fed. Cir. 2008)). The Tsinontides manuscript does not describe any steps, the details of those steps, or the order of those steps. There is no mention of any process involving "[c]harging a solution of carbon dioxide source, having a pH range of about 6.0 to about 12.0 into a reaction vessel." (PTX 2 at 18:33-35). The presentation similarly fails to disclose "adding an effective amount of a mole ratio of a base and an active ingredient into the reaction vessel containing the solution of a carbon dioxide source." (*Id.* at 18:36-38). The manuscript sheds some light on the process ultimately claimed in the '150 patent, but it does not disclose the elements of claim 21. (Tr. 938:19-941:6).

Since the Tsinontides manuscript does not anticipate claim 21, it cannot anticipate claims 22 through 29, which depend from claim 21. *See Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012) ("[A] dependent claim narrows the claim from which it depends [and] must 'incorporate . . . all the limitations of the claim to which it refers.'" (omission in original) (quoting 35 U.S.C. 112 ¶ 4)).

Therefore, Defendant has failed to show, by clear and convincing evidence, that the Tsinontides manuscript anticipates claims 21 through 29 of the '150 patent.

III. CONCLUSION

Defendant failed to prove by clear and convincing evidence that any of the asserted claims of the '323 patent are invalid. Defendant proved by clear and convincing evidence that asserted claims 21 through 34 of the '150 patent are invalid as obvious.

Plaintiff should submit an agreed upon form of final judgment within two weeks.


US006486150B2

(12) **United States Patent**
Hunke et al.

(10) **Patent No.: US 6,486,150 B2**
(45) **Date of Patent: Nov. 26, 2002**

(54) **PROCESS FOR FORMULATION OF ANTIBIOTIC COMPOUNDS**

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Related U.S. Application Data

(63) Continuation-in-part of application No. 09/698,808, filed on Oct. 27, 2000.
(60) Provisional application No. 60/162,482, filed on Oct. 29, 1999.

(51) **Int. Cl.**[7] **A61K 31/407**
(52) **U.S. Cl.** **514/210.13**; 540/350
(58) **Field of Search** 514/210.13; 540/350

(56) **References Cited**

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5,652,233 A 7/1997 Betts et al.
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6,297,231 B1 * 10/2001 Almarsson et al. 514/210.13

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WO WO 93/15078 8/1993

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Betts et al., Chem. Abs. 118: 80721, 1992.
Peter A. S. Smith, The Chemistry of Open–Chain Organic Nitrogen Compounds, vol. 1, p. 263, 1965.

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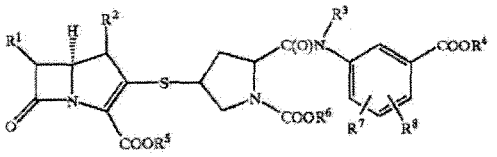
(57) **ABSTRACT**

The present invention involves a process for preparing a stable final formulation product of a compound of formula I,

I



or its pharmaceutically acceptable salt, hydrate or solvate by incorporating a suitable carbon dioxide source to an unstable monosodium adduct of carbapenem antibiotic compound.

40 Claims, No Drawings

PROCESS FOR FORMULATION OF ANTIBIOTIC COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part (CIP) application of U.S. Ser. No. 09/698,808, filed Oct. 27, 2000, which claims the benefit of Provisional application Ser. No. 60/162,482, filed Oct. 29, 1999.

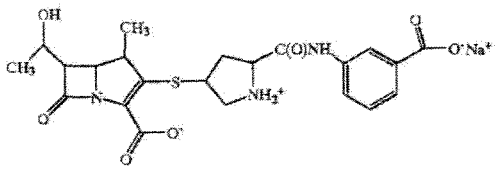
FIELD OF THE INVENTION

The present invention relates to a process for preparing a stabilized form of antibiotic compounds, in particular a carbapenem antibiotic composition.

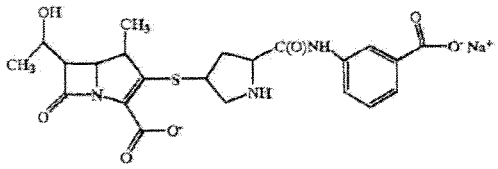
BACKGROUND OF THE INVENTION

Betalactams, a broader class of antibiotics which is further defined as carbapenems are useful for the treatment of infectious diseases including gram positive and negative, and aerobic and anaerobic bacteria. Carbapenems were first isolated from fermentation media in 1974 and were found to have broad-spectrum antibacterial activity. Since this discovery substantial investigations have been made into new carbapenem derivatives and many hundreds of patents and scientific papers have been published. The commercially marketed carbapenem is imipenem (N-formimidoyl thienamycin), which has a broad range of antibacterial activity. This compound can be used in the treatment of any disease that is conventionally treated with antibiotics, for example in the treatment of bacterial infection in mammals including humans.

It has been reported that dimerization of carbapenem is inhibited via the formation of a reversible equilibrium adduct between carbon dioxide and monosodium salt of carbapenem compound as shown below, where K_a and K_{eq} are equilibrium constants of the reactions.



K_a



K_{eq}

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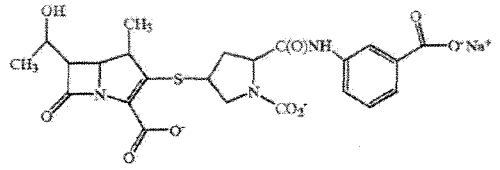


During the manufacture of bulk antibiotic products such as carbapenem antibiotic, the pharmaceutical compound is prepared by chemical synthesis from raw materials in large quantities. Carbapenem antibiotic compounds are prepared in large batches as salt form, monosodium salt as shown above, which are weak crystalline solids, hygroscopic at ambient conditions, and unstable at room and refrigerated temperatures. Because the compound is unstable at a temperature above about −20° C., the bulk compounds must be stored at a low temperature (about −20° C.) to prevent degradation into dimers or open ring by-products. Although the unstable compound of carbapenem, after bulk manufacturing, can be stored for long periods of time at a low temperature, it must be converted into a stable formulation prior to use as once-a-day antimicrobial agent for intravenous (IV) or intramuscular (IM) administration.

Several reported cases for preparing carbapenem antibiotic compounds have shortcomings of teaching how to achieve a stable form of carbapenem antibiotics in its final formulation and manufacturing process. In particular, they fail to teach how to achieve the conversion of salt-containing carbapenem compound to a formulation exhibiting acceptable levels of degradates required for solid state and reconstitution stability for dosing to patients.

For example, Almarsson et al. (WO 98/18800) discloses a method for stabilizing carbapenem antibiotics by carboxylating the pyrrolidinyl amino acid with a carbon dioxide source, but fails to teach the steps necessary to obtain the stable form of carbapenem during its formulation process.

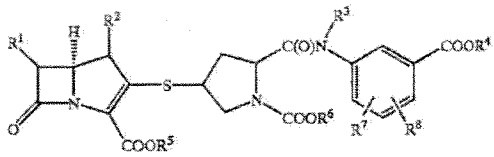
Zimmerman et al. (U.S. Pat. No. 5,952,323) relates a method of stabilizing a carbapenem compound by incorporating carbon dioxide source, but it also does not provide how to achieve the stabilized form of carbon dioxide adduct in its final composition.

In light of the above, an objective of the present invention is to provide a process for formulating a final product of stable antibiotic compound, in particular carbapenem antibiotic for the treatment of infectious diseases which include gram positive and negative, and aerobic and anaerobic bacteria. Another object of the present invention is to provide a novel manufacturing process to prepare the final formulation product of carbapenem antibiotic with acceptable levels of degradates, solid state stability and solution stability for dosing.

SUMMARY OF THE INVENTION

The present invention is directed to a process for preparing a final formulation product of a compound of Formula I,

I



or its pharmaceutically acceptable salt, hydrate or solvate wherein,

R^1 is:

(a) 1-hydroxyethyl,

(b) 1-fluoroethyl, or

(c) hydroxymethyl;

R^2 and R^3 are independently:

(a) hydrogen, or

(b) $(C_1–C_6)$-alkyl;

R^4, R^5 and R^6 are independently

(a) hydrogen

(b) $(C_1–C_6)$-alkyl, or

(c) alkali-metal or alkali earth-metal wherein the alkali-metal or alkali earth-metal is sodium, potassium, lithium, cesium, rubidium, barium, calcium or magnesium; and

R^7 and R^8 are independently:

(a) hydrogen,

(b) halo,

(c) cyano,

(d) $(C_1–C_6)$-alkyl,

(e) nitro,

(f) hydroxy,

(g) carboxy,

(h) $(C_1–C_6)$-alkoxy,

(i) $(C_1–C_6)$-alkoxycarbonyl,

(j) aminosulphonyl,

(k) $(C_1–C_6)$-alkylaminosulphonyl,

(l) di-$(C_1–C_6)$-alkylaminosulphonyl,

(m) carbamoyl,

(n) $(C_1–C_6)$-alkylcarbamoyl,

(o) di-$(C_1–C_6)$-alkylcarbamoyl,

(p) trifluoromethyl,

(q) sulphonic acid,

(r) amino,

(s) $(C_1–C_6)$-alkylamino,

(t) di-$(C_1–C_6)$-alkylmino,

(u) $(C_1–C_6)$-alkanoylamino,

(v) $(C_1–C_6)$-alkanoyl(N-$(C_1–C_6)$-alkyl)amino,

(w) $(C_1–C_6)$-alkanesulphonamido, or

(x) $(C_1–C_6)$-alkyl-S(O)$_n$ wherein n is 0–2;

comprising the steps of:

(1) charging a solution of carbon dioxide source having a pH range of about 6.0 to about 12.0 into a reaction vessel;

(2) adding an effective amount of a mole ratio of a base and an active ingredient into the reaction vessel containing the solution of carbon dioxide source to maintain pH at about 6.0 to about 9.0 and a temperature range of about −3° C. to about 15° C.;

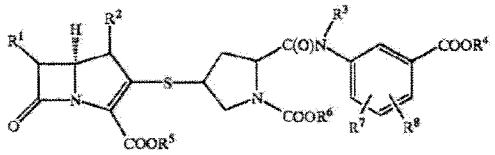
(3) lyophilizing the solution of Step (2) to yield the final formulation product of a compound of formula I with less than about 10% of moisture content.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a process for preparing a stable form of carbapenem compound in its formulation and manufacturing processes. More specifically, the present invention involves a process for preparing a stabilized carbon dioxide adduct of carbapenem antibiotic by incorporating suitable carbon dioxide source to unstable salt form of carbapenem antibiotic, in particular monosodium salt of carbapenem, at suitable reaction conditions. The stable carbon dioxide adduct of the carbapenem antibiotic formulation is useful for the treatment of bacterial infections in mammal patients, which can be administered intravenously or intramuscularly.

The present invention is directed to a process for preparing a final formulation product of a compound of Formula I,

I



or its pharmaceutically acceptable salt, hydrate or solvate wherein,

R^1 is:

(a) 1-hydroxyethyl,

(b) 1-fluoroethyl, or

(c) hydroxymethyl;

R^2 and R^3 are independently:

(a) hydrogen, or

(b) $(C_1–C_6)$-alkyl;

R^4, R^5, and R^6 are independently

(a) hydrogen

(b) $(C_1–C_6)$-alkyl, or

(c) alkali-metal or alkali earth-metal wherein the alkali-metal or alkali earth-metal is sodium, potassium, lithium, cesium, rubidium, barium, calcium or magnesium; and

R^7 and R^8 are independently:

(a) hydrogen,

(b) halo,

(c) cyano,

(d) $(C_1–C_6)$-alkyl,

(e) nitro,

(f) hydroxy,

(g) carboxy,

(h) $(C_1–C_6)$-alkoxy,

(i) $(C_1–C_6)$-alkoxycarbonyl,

(j) aminosulphonyl,

(k) $(C_1–C_6)$-alkylaminosulphonyl,

(l) di-$(C_1–C_6)$-alkylaminosulphonyl,

(m) carbamoyl,

(n) $(C_1–C_6)$-alkylcarbamoyl,

(o) di-(C_1–C_6)-alkylcarbamoyl,

(p) trifluoromethyl,

(q) sulphonic acid,

(r) amino,

(s) (C_1–C_6)-alkylamino,

(t) di-(C_1–C_6)-alkylmino,

(u) (C_1–C_6)-alkanoylamino,

(v) (C_1–C_6)-alkanoyl(N-(C_1–C_6)-alkyl)amino,

(w) (C_1–C_6)-alkanesulphonamido, or

(x) (C_1–C_6)-alkyl-S(O)$_n$ wherein n is 0–2;

comprising the steps of:

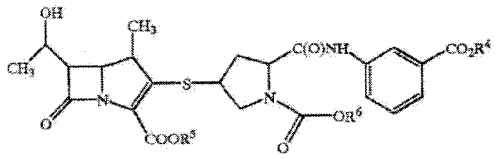
(1) charging a solution of carbon dioxide source having a pH range of about 6.0 to about 12.0 into a reaction vessel;

(2) adding an effective amount of a mole ratio of a base and an active ingredient into the reaction vessel containing the solution of carbon dioxide source to maintain pH at about 6.0 to about 9.0 and a temperature range of about −3° C. to about 15° C.;

(3) lyophilizing the solution of Step (2) to yield the final formulation product of a compound of formula I with less than about 10% of moisture content.

A preferred embodiment of the present invention is a process for preparing a formulation of a compound of Formula Ia,

Ia



or its pharmaceutically acceptable salt, hydrates or solvate wherein,

R^4, R^5, and R^6 are independently:

(a) hydrogen

(b) (C_1–C_6)-alkyl, or

(c) alkali-metal or alkali earth-metal wherein the alkali-metal or alkali earth-metal is sodium, potassium, lithium, cesium, rubidium, barium, calcium or magnesium;

comprising the steps of:

(1) charging a solution of carbon dioxide source having a pH range of about 6.0 to about 12.0 into a reaction vessel;

(2) adding an effective amount of a mole ratio of a base and an active ingredient into the reaction vessel containing the solution of carbon dioxide source to maintain pH at about 6.0 to about 9.0 and a temperature range of about −3° C. to about 15° C.;

(3) lyophilizing the solution of Step (2) to yield the final formulation product of a compound of formula I with less than about 10% of moisture content.

An aspect of the process as recited above is where the carbon dioxide source is selected from the group consisting of carbon dioxide, sodium bicarbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, calcium carbonate, cesium carbonate, magnesium carbonate, lithium carbonate, and a mixture thereof. The preferred carbon dioxide source is sodium bicarbonate.

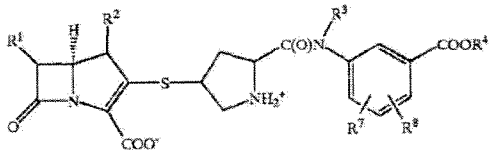
Another aspect of the process recited above is where the carbon dioxide source in Step (1) is present in an amount relative to the amount of active ingredient, wherein a mole ratio of carbon dioxide source to the active ingredient is about 0.5 to about 1.5, preferably about 0.8 to about 1.2.

Yet another aspect of the process as recited above is where the pH range in Step (1) is about 7.0 to about 9.0.

Still another aspect of the process as recited above is where a temperature range in Step (1) is about −3° C. to about 15° C.

Still another aspect of the process as recited above is where the active ingredient is a compound of formula (a),

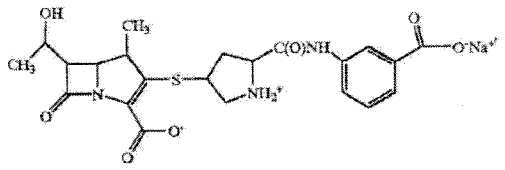
(a)



wherein R^1, R^2, R^3, R^4, R^7 and R^8 are as defined above.

Still another aspect of the process as recited above is where the preferred active ingredient is a compound of formula (a)'

(a)'



Another aspect of the process as recited above is where the base is selected from the group consisting of sodium hydroxide, lithium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide, magnesium hydroxide, lithium methoxide, sodium methoxide, potassium methoxide, calcium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium tert-butoxide, sodium tert-butoxide and potassium tert-butoxide.

Yet another aspect of the process as recited above is where the base is sodium hydroxide at a concentration range of about 1N to about 3N.

Still another aspect of the process as recited above is where the effective amount of a mole ratio of a base to an active ingredient in Step (2) is about 0.7 to about 1.0.

Still another aspect of the process as recited above is where the mole ratio of a base to an active ingredient in Step (2) is about 0.8 to about 0.9.

Still another aspect of the process as recited above is where the pH range in Step (2) is about 7.0 to about 8.0.

Still another aspect of the process as recited above is where the temperature range in Step (2) is about −1° C. to about 5° C.

Still another aspect of the process as recited above is where the base is added followed by the addition of the active ingredient in Step (2).

Still another aspect of the process as recited above is where the temperature range in Step (2) is about −1° C. to about 5° C.

Still another aspect of the process as recited above is where the Step (2) further comprises a titration of the

solution using a titrating agent to maintain the pH of the solution at a range of about 6.5 to about 8.5.

Still another aspect of the process as recited above is where the titrating agent is selected from the group consisting of sodium hydroxide, lithium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide, magnesium hydroxide, lithium methoxide, sodium methoxide, potassium methoxide, calcium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium tert-butoxide, sodium tert-butoxide and potassium tert-butoxide.

Still another aspect of the process as recited above is where the moisture content of the final formulation product is less than about 5%.

Still another aspect of the process as recited above is where the step (3) initially further comprises the following steps of:

(a) filtering the final formulation product into a receiving vessel using a sterilizing filter;

(b) aseptically filling the filtered final formulation product into a sterile vial; and

(c) placing a lyophilization stopper on the filled sterile vial containing the final formulation product.

It is further understood that the substituents recited above would include the definitions recited below, and unless otherwise stated or indicated, the definitions shall apply throughout the specification and claims.

As used herein, the term "alkyl" includes those alkyls of a designated number of carbon atoms of either a straight, branched or cyclic configuration. Examples of "alkyl" includes but are not limited to: methyl (Me), ethyl (Et), propyl, butyl, pentyl, hexyl, heptyl, octyl, nonanyl, decyl, undecyl, dodecyl, and the isomers thereof such as isopropyl (i-Pr), isobutyl (i-Bu), sec-butyl (s-Bu), tert-butyl (t-Bu), isopentane, isohexane, and the like.

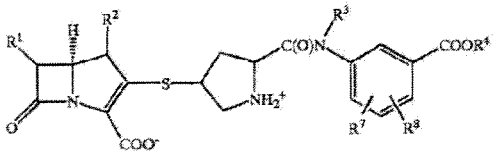
The term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, and the like.

The term "halogen" or "halo" refer to fluorine, chlorine, bromine and iodine.

As used herein, the term "1 mole equivalent" is defined as 1 mole of carbon dioxide source per 1 mole of active ingredient (or active drug), wherein carbon dioxide source includes carbon dioxide, sodium bicarbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, calcium carbonate, cesium carbonate, magnesium carbonate, lithium carbonate, and a mixture thereof.

The term "active ingredient," also refers to as "bulk drug," "bulk active drug," "bulk active beta-lactam" or "bulk active carbapenem," refers to the amount of actual unstable, beta-lactam, carbapenem and/or alkali-metal salt or alkali earth-metal salt containing carbapenem removed from cold storage. The preferred active ingredient is a compound of formula of (a),

(a)



wherein

R^1 is:

(a) 1-hydroxyethyl,

(b) 1-fluoroethyl, or

(c) hydroxymethyl;

R^2 and R^3 are independently:

(a) hydrogen, or

(b) $(C_1–C_6)$-alkyl;

R^4, R^5, and R^6 are independently

(a) hydrogen

(b) $(C_1–C_6)$-alkyl, or

(c) alkali-metal or alkali earth-metal wherein the alkali-metal or alkali earth-metal is sodium, potassium, lithium, cesium, rubidium, barium, calcium or magnesium; and

R^7 and R^8 are independently:

(a) hydrogen,

(b) halo,

(c) cyano,

(d) $(C_1–C_6)$-alkyl,

(e) nitro,

(f) hydroxy,

(g) carboxy,

(h) $(C_1–C_6)$-alkoxy,

(i) $(C_1–C_6)$-alkoxycarbonyl,

(j) aminosulphonyl,

(k) $(C_1–C_6)$-alkylaminosulphonyl,

(l) di-$(C_1–C_6)$-alkylaminosulphonyl,

(m) carbamoyl,

(n) $(C_1–C_6)$-alkylcarbamoyl,

(o) di-$(C_1–C_6)$-alkylcarbamoyl,

(p) trifluoromethyl,

(q) sulphonic acid,

(r) amino,

(s) $(C_1–C_6)$-alkylamino,

(t) di-$(C_1–C_6)$-alkylmino,

(u) $(C_1–C_6)$-alkanoylamino,

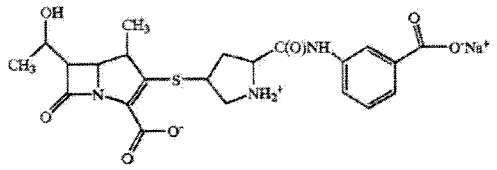
(v) $(C_1–C_6)$-alkanoyl(N-$(C_1–C_6)$-alkyl)amino,

(w) $(C_1–C_6)$-alkanesulphonamido, or

(x) $(C_1–C_6)$-alkyl-$S(O)_n$ wherein n is 0–2;

The most preferred active ingredient is a compound of formula of (a)',

(a)'



The term "active drug," as used herein, is defined as the actual amount of beta-lactam, unstabilized and stabilized carbapenem, and alkali metal salt-containing carbapenem and carbon dioxide-containing carbapenem.

The term "quantum sufficit" ("q.s."), as used herein, is defined as the amount of a reagent necessary to increase the batch weight or volume to a specified total. As an example, a q.s. of 95% by wt % means the amount of reagent required to bring the weight percent up to 95% by weight based on 100% total weight.

The term "solid state stability" is defined as the ability of finished solid and lyophilized formulation (a porous off-white cake) at the end of about 2 years to deliver the prescribed and labeled dosage of active drug.

The term "reconstitution stability" is defined as the ability of a solution prepared by the finished solid and lyophilized formulation into an appropriate diluent (i.e. 0.9% saline for injection, 1% Lidocaine, and etc.) to deliver the prescribed and labeled dosage of active drug.

The batch-wise process of the present invention is carried out under aseptic conditions and requires several reagents and processing units to prepare formulations of high pharmaceutical quality. The present process provide a high rate conversion from the alkali metal salt, such as monosodium salt of carbapenem to the carbon dioxide adduct and the low by-product formation, such as dimers and open ring compounds. The reaction parameters and conditions such as the mole ratio of carbon dioxide source and active ingredient, mole ratio of base and active ingredient (active bulk carbapenem), reaction temperatures, pH of the solution, proper mixing, and appropriate lyophilization parameters are critical to obtain a final formulation product of high pharmaceutical quality.

The process for preparing a stable intravenous formulation of a carbon dioxide adduct of a carbapenem requires the processing temperature of about −3° C. to about 15° C., preferably about −1° C. to about 5° C., and the pH of the pre-lyophilized active solution to be about 6.0 to about 12.0, preferably about 7.0 to about 9.0. The process is carried out under aseptic conditions. All reagents used during the present processes meet *United States Pharmacopeia and National Formulary* standards unless otherwise stated.

Methods of preparing the compound of the present invention are illustrated in the following process and examples. They are provided for illustrative purposes and should not be construed as limiting the invention disclosed herein.

PROCESS

Sodium hydroxide solution of about 1N to about 3N is prepared by dissolving a sufficient amount of sodium hydroxide NF pellets in a sufficient amount of Water For Injection (WFI). While adding the sodium hydroxide, the solution is constantly mixed to ensure complete dissolution. The compounder/reactor (200L stainless steel jacketed vessel) is jacketed and cooled to maintain at a low temperature to prevent bulk drug degradation during the process. A variable agitation system is attached to the compounder/reactor to ensure complete dissolution of the bulk drug into solution. Generally, about 40% by weight or 60% by volume of WFI is charged into the compounder/ reactor to begin the process, and the water is cooled to the temperature range of about −3° C. to about 15° C., preferably about −1° C. to about 5° C. To measure the pH of the solution in the compounder/reactor, appropriate pH and temperature devices are used. The pH meter is typically calibrated with buffer solution of pH 7.0 and 10.0. To maintain the pH of the solution within the required range during the batch-wise process, an appropriate pH controller system equipped with a pump is utilized to meter sodium hydroxide solution into the compounder/reactor.

After the WFI in the compounder/reactor is cooled, mixing is commenced to prevent localization of pH, temperature, and concentration of reagents and bulk antibiotic drug. A sufficient amount of carbon dioxide source such as sodium bicarbonate and/or sodium carbonate is added to the compounder/reactor under continuous mixing of the WFI to provide a final formulation concentration of about one mole equivalent (a mole ratio of carbon dioxide source to the active ingredient is about 0.5 to about 1.5, preferably about 0.8 to about 1.2). The solution is mixed until the carbon dioxide source, such as carbonates are completely dissolved. The pH of the solution is measured to ensure that it is about 6.0 to about 12.0, preferably about 7.0 to about 9.0 at a temperature range of about −3° C. to about 15° C. It is preferred that the temperature and pH of the solution be confirmed prior to beginning the addition of bulk drug. The unstable bulk carbapenem drug is removed from a refrigerated unit held at about −20° C. or lower and may be thawed to a temperature of from about 5° C. to about 25° C. for about 1 hour. A sufficient amount of the bulk drug is weighted out to provide a final formulation concentration of carbapenem to be about 200 g of active drug (as free acid)/liter formulation.

During the addition of the bulk active carbapenem to the compounder/reactor, the carbonate solution is constantly mixed. Generally, the mixing begins at lower agitation speed during the initial addition of bulk drug to the solution and as the amount of bulk in the solution is increased, mixing may be increased proportionally thereto. The primary purpose of mixing is to ensure complete dissolution of the bulk drug into the solution. As necessary, sodium hydroxide solution is added to the compounder/reactor during the addition of the bulk drug to maintain the pH of the solution to be about 6.0 to about 9.0, preferably about 7.0 to about 8.0. The bulk drug is generally slowly added to the compounder/reactor at a constant rate for about 30 minutes to about 90 minutes to enhance dissolution. At the end of the bulk drug addition, the solution is mixed for additional few minutes to ensure complete dissolution. The q.s. of the batch weight is adjusted to about 95% by weight of the final weight of the formulation with WFI, if needed, while maintaining the temperature at about −1° C. and about 5° C. Further titration using sodium hydroxide may be performed over a 10 minute to 20 minute period to ensure a mole ratio of base (NaOH) and bulk active drug to be in the range of from about 0.7 to about 1.0, preferably about 0.8 to about 0.9. Finally, the batch is adjusted to 100% by weight of its final weight with WFI with moderate mixing.

Afterwards, the solution is filtered through a sterilizing filter such as that from about 0.2 μm to about 0.25 μm. When making larger batches, generally from about 10L to about 200L in a compounder/rector, the compounding vessel is sealed and pressurized to initiate filtration. Filtration can be done either by pumping the solution through sterilizing filters with an appropriate pump in the absence of compounding vessel that can be pressurized or appropriate gas to carry out filtration by pressure. The receiving vessel should be sterile and cooled to a temperature range of about −3° C. to about 15° C. The density of the filtered formulation solution is generally about 1.0 g/mL to about 1.2 g/mL at about 0° C. to about 5° C., typically about 1.1 g/mL. Lyophilization of the completed formulation is preferred to simplified manufacture. However, the solution could be bulk lyophilized and the resulting powder filled into packages for use. If the processed by lyophilization in vials, the filtered formulation can be filled into vials and partially sealed with dry sterile siliconized lyophilization stoppers. In the following examples conventional 20 mL vials and 15 mL ADD-Vantage™ vials are utilized. The vials are filled at specified target fill and then placed onto lyophilizer shelves, which are pre-cooled to a temperature of about −40° C. to about −45° C., typically about −40° C. Suitable lyophilization cycle is then run with vials.

The lyophilization cycles used herein for the different vials are described in the examples below. Generally, the

cycle requires the vials to be soaked at about −40° C. for about two hours and then heated to a temperature range of about −25° C. to about −15° C. shelf temperature at a rate of about 0.5° C./minute. The temperature is normally maintained at about −25° C. to about −15° C., and the pressure of the lyophilizer chamber is maintained at about 80 mTorr for about 48 hours to about 60 hours. The vials are heated to about 10° C. shelf temperature at a rate of about 0.1° C./minute and then to about 40° C. shelf temperature at a rate of about 0.5° C./minute, and maintained at 40° C. for up to about three hours at a pressure of about 80 mTorr or lower. The vials are then heated to about 60° C. shelf temperature at a rate of about 0.5° C./minute and held there at about 80 mTorr or less for about 3 hours to about 10 hours. The shelves are then cooled to ambient temperature (about 20° C.–30° C.). The vials are completely sealed under a partial vacuum of about 0.9 bar/700 Torr or lower before removing them from the lyophilizer. The vials are stored at a temperature not exceeding about 25° C. until needed.

EXAMPLE 1

At ambient temperature and pressure, a 2N sodium hydroxide solution was prepared by dissolving 20 g of sodium hydroxide NF pellets in 250 mL of water for injection (WFI) while mixing. A Beckman pH probe was calibrated using pH 7 and pH 10 buffers. Into a Kontes 317000–1000, one (1) liter glass, compounder/reactor vessel with jacketed cooler and agitator was charged 400 mL of WFI (about 50% of total batch volume), which was cooled to about 5° C. Thereafter, 28.0 g of sodium bicarbonate were dissolved into the compounder/reactor, and the compounder/reactor was held at a temperature of between about 1° C. and about 5° C., and a pH of between about 8.1 and about 8.5.

About 160 g of free acid, which is calculated from monosodium salt of carbapenem, exhibiting a moisture content of about 17.0% by weight were thawed to room temperature from −20° C. for about 30 minutes. The bulk drug was divided into ten equal portions and was gradually added to the sodium bicarbonate solution along with 2N NaOH solution for about 60 minutes to ensure complete dissolution. To reduce localization of pH, the 2N solution of sodium hydroxide was metered sub-surface into the compounder/reactor by a Masterflex peristaltic pump through size 16 tubing and a one foot long×1/16 inches diameter stainless steel dip tube. During the addition of the bulk drug and NaOH, the formulation solution was constantly agitated. The solution temperature was maintained between about 1° C. and about 6° C. and the pH at a set point of about 7.8 by adding sodium hydroxide solution. Following the addition of the bulk drug, the batch weight was adjusted to 95% of the final weight with WFI maintained at a temperature of about −1° C. to 5° C. to produce a bulk drug-sodium bicarbonate solution. While the bulk drug-sodium bicarbonate solution was agitated for an additional 20 minutes, 2N sodium hydroxide titration was performed that resulted in a mole ratio of sodium hydroxide to bulk drug of about 0.93. The final weight of the batch was adjusted to 100% total with chilled WFI at about −1° C. to about 5° C. with additional agitation for about 5 minutes. The total drug addition and compounding time was about 102 minutes, and the final batch weight was about 888.0 g.

While maintaining the solution at a temperature range of about −1° C. and about 5° C., the bulk drug-sodium bicarbonate solution was filtered utilizing a Sterivex GV filter unit containing a 0.22 μm filter into a sterile plastic container using a peristaltic pump. Immediately thereafter, about 6.33 g of the solution was placed into conventional 20 mL vials utilizing a manual filler, and the vials were frozen to about −70° C. The vials were partially stoppered and placed onto the shelves of a Virtis Lyophilizer pre-cooled to about −40° C. The lyophilizer was then operated according to the following cycle:

a) soak at about −40° C. shelf temperature for about two hours;

b) heat to about −20° C. shelf temperature at rate of about 0.5° C./min.;

c) hold shelf temperature at about −20° C. and about 80 mTorr pressure for about 48 hours;

d) heat to about 10° C. shelf temperature at rate of about 0.1° C./min;

e) heat to about 40° C. shelf temperature at rate of about 0.5° C./min.;

f) hold at about 40° C. and about 80 mTorr for about three hours;

g) heat to about 60° C. shelf temperature at rate of about 0.6° C./min.;

h) hold at about 60° C. and about 80 mTorr for about three hours;

i) cool the shelves to ambient temperature (about 20° C.–30° C.); and

j) stopper under partial vacuum of about 0.9 bar/700 Torr.

Finally, the vials were removed from the lyophilizer as the final formulation. Table 1 provides the analysis results of the final formulation product.

TABLE 1

Analysis of the formulation product

component	g/L	g/0.8 L
carbapenem	200.0[a]	160.0[a]
sodium bicarbonate	35.0	28.0
sodium hydroxide[b]	adjusted to pH 7.8	adjusted to pH 7.8
water for injection[c]	q.s 1.00 L	q.s. 0.8 L[d]

[a]as free acid
[b]diluted in Water for Injection, and used as 2N solution for pH control
[c]removed during lyophilization
[d]q.s. 0.89 Kg based on 1.11 g/mL solution density

The final product exhibited moisture content of about 1.91% w/w.

Table 2 illustrates the High Performance Liquid Chromatography (HPLC) results in area % of in process samples collected during the production of stabilized carbapenem antibiotic for this example.

TABLE 2

HPLC analysis of in-process samples

	Carbapenem	Total Degradates	Total Dimers	Ring Open
	HPLC, Area %			
bulk drug	98.6	1.4	0.5	0.7
prefilter solution.	97.6	2.3	1.1	1.0
end of vial filling	96.8	3.0	1.5	1.4
lyophilized product	95.6	4.4	1.6	2.5

EXAMPLE 2

The general procedure described in Example 1 was utilized to prepare the formulation of this example. Except for

the parameter values provided in Table 3, identical conditions were applied in both examples. The final product exhibited moisture content of about 1.9% w/w. Table 4 illustrates the HPLC results in area % of in-process samples collected during the production of stabilized carbapenem antibiotic for this example.

TABLE 3

Compounding conditions	
drug addition time (min.)	30
total compounding time (min.)	68
pH set point during compounding	7.4
mole ratio of NaOH/Drug	0.83

TABLE 4

HPLC analysis of in-process samples

Image	Carbapenem	Total Degradates	Total Dimers	Ring Open
	HPLC, Area %			
carbapenem prefilter solution	98.5	1.5	0.7	0.7
	98	1.9	0.9	0.9
end of fill	97.3	2.5	1.2	1.2
lyophilized product	95.9	4.1	1.5	2.3

EXAMPLES 3 AND 4

Examples 3 and 4 were carried out according to the same basic procedures described below with the exception of the parameters given in Table 5. The vials utilized in Example 3 were conventional 20 mL vials, whereas those utilized in Example 4 were ADD-Vantage™ 15 mL vials.

TABLE 5

Reaction conditions

Image	Example 3	Example 4
drug addition time (min.)	45	66
total compounding time (min.)	114	134
pH controller set point during drug addition	7.6	7.6
pH controller set point during pH adjustment	7.7	7.7
mole ratio of NaOH added to active drug	0.85	0.87
filtration time (min.)	30	31
vial filling time (min.)	203	157
lyophilizer cycle time (min.)	65	78

To prepare a pilot plant batch of the formulation, a 2N solution of sodium hydroxide was prepared by dissolving about 250 g of sodium hydroxide NF pellets in about 2000 g of WFI. While mixing, the solution was cooled to ambient temperature, and WFI was added to produce the final solution of about 3406 g. The sodium hydroxide solution was then chilled by using an Isotemp 1028S Chiller to a temperature of about 4° C. Into a 20L-stainless steel jacketed compounder/reactor, about 6.42 kg of the WFI was charged, and the solution was cooled to a target temperature of about −20° C. to about 5° C. The pH probe attached to a HD-PH-P pH Controller was standardized using pH 7.0 and pH 10.0 buffer solutions.

About 448 g of sodium bicarbonate was completely dissolved in the compounder/reactor, and the pH of the solution was measured at about 8.3. About 2560 g of unstabilized bulk drug (as free acid) was thawed from −20° C. to ambient temperature for approximately one hour and then divided into 10 equal portions. The 10 portions of bulk drug were added to the compounder/reactor for about 60 minutes while adding the sodium hydroxide solution via the pH controller to maintain the pH of bulk drug solution at about 7.6. At the end of the bulk drug addition, the solution was mixed for additional 15 minutes, and 2N NaOH titration was preformed to confirm complete dissolution of the bulk drug. After mixing again for another 15 minutes, water for injection at a temperature of about 0° C. to about 8° C. was added to bring the solution to about 97% of the total weight based on 100 total weight percent. While still mixing the solution, the pH was adjusted to about 7.7 with 2N NaOH solution to ensure that the mole ration of base (NaOH) to the bulk drug is within the range of about 0.8 to about 0.9. The weight of the solution was adjusted to 100 weight percent of the final batch weight by adding WFI at about 0° C. to about 8° C. while mixing for another five minutes. The compounder/reactor was then sealed and pressurized to about 15 psig to initiate filtration. The solution was then filtered through a Millipak 0.22 μm sterilizing filter into a sterile receiving vessel, which is continuously cooled to a temperature of about −1° C. to about 5° C. The filtered formulation solution exhibited a density of about 1.11 g/mL at about 5° C.

The sterile formulation was placed into sterile glass vials (6.33 g into 20 mL conventional vials, and 5.77 g into 15 mL ADD-Vantage™). The filled vials were partially stoppered with dry sterile siliconized lyophilization stoppers and placed onto lyophilizer shelves, which are pre-cooled to a temperature of about −45° C. to about −40° C. The lyophilizing procedure was conducted as follows:

20 mL Conventional Vials

a) soak at about −40° C. (about −45° C. to −40° C.) lyo shelf temperature for at least two hours;

b) heat to about −20° C. shelf temperature at about 0.5° C./minute;

c) hold shelf temperature at about −20° C. and about 80 mTorr pressure for about 48 hours;

d) heat to about 10° C. shelf temperature at about 0.1° C./minute;

e) heat to about 40° C. shelf temperature at about 0.5° C./minute, and hold at about 40° C. and about 80 mTorr for about 3 hours;

f) heat to about 60° C. shelf temperature at 0.5° C./minute, and hold at about 60° C. and about 80 mTorr for about 3 hours;

g) cool the shelves to ambient temperature (about 20° C.–30° C.) before unloading; and

h) stopper under partial vacuum (target of about 0.9 bar/700 Torr).

ADD-Vantage™ Vials

a) soak at about −40° C. (about −45° to −40° C.) lyophilizer shelf temperature for at least 2 hours;

b) heat to about −20° C. shelf temperature at about 0.5° C./minute;

c) hold shelf temperature at about −20° C. and about 80 mTorr pressure for about 54 hours;

d) heat to about −10° C. shelf temperature at about 0.1° C./minute, and hold at about −10° C. and about 80 mTorr for about 4 hours;

c) heat to about 10° C. shelf temperature at about 0.1° C./minute;

f) heat to about 40° C. shelf temperature at about 0.5° C./minute, and hold at about 40° C. and about 80 mTorr for about 3 hours;

g) heat to about 60° C. shelf temperature at about 0.5° C./minute, and hold at about 60° C. and about 80 mTorr for about 3 hours;

h) cool the shelves to ambient temperature (about 20° C.–30° C.) before unloading; and

i) stopper under partial vacuum (target of about 0.9 bar/700 Torr).

After completion of the lyophilizing step, the vials containing the formulation were removed from the lyophilizer and capped (flip-off caps for conventional vials and ADD-Vantage caps for ADD-Vantage vials). The vials were then stored at a temperature of about 25° C. or below. Table 6 provide the analysis results of the final stabilized carbapenem antibiotic formulation.

TABLE 6

Analysis results of stabilized carbapenem antibiotic

Component	g/L	g/12.8 L
carbapenem	200.0	2560
sodium bicarbonate	35.0	448
sodium hydroxide	adjusted to pH 7.5	adjusted to pH 7.5
WFI	q.s. 1.00 L	q.s. 12.8 L

Table 7 summarizes the HPLC results of area % of in-processing samples collected during production of the batch of Example 3.

TABLE 7

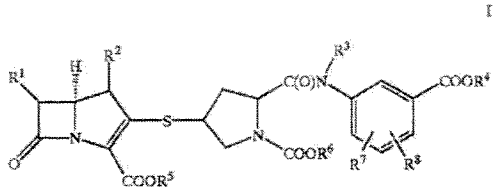
HPLC analysis of in-process samples

	Carbapenem	Total Degradates	Total Dimers	Ring Opening
	HPLC, Area %			
bulk carbapenem	99.2	0.7	0.4	0.3
pre-filtered solution	97.6	2.2	1.0	1.2
beginning of vial filling	96.9	3.0	1.6	1.4
middle of vial filling	96.3	3.0	1.6	1.4
end of vial filling	95.7	4.3	2.5	1.7
beginning of lyophilization	95.5	4.4	1.7	2.5
middle of lyophilization	95.2	4.6	1.9	2.5
end of lyophilization	94.7	5.2	2.3	2.7

The final product moisture, as determined by NIR for Examples 3 and 4 were about 1.8% and about 2.1%, respectively.

What is claimed is:

1. A process for preparing a final formulation product of a compound of formula I,



I

or its pharmaceutically acceptable salt, or hydrate wherein,

R^1 is:
- (a) 1-hydroxyethyl,
- (b) 1-fluoroethyl, or
- (c) hydroxymethyl;

R^2 and R^3 are independently:
- (a) hydrogen, or
- (b) $(C_1–C_6)$-alkyl;

R^4, R^5, and R^6 are independently
- (a) hydrogen
- (b) $(C_1–C_6)$-alkyl, or
- (c) alkali-metal or alkali earth-metal wherein the alkali-metal or alkali earth-metal is sodium, potassium, lithium, cesium, rubidium, barium, calcium or magnesium; and

R^7 and R^8 are independently:
- (a) hydrogen,
- (b) halo,
- (c) cyano,
- (d) $(C_1–C_6)$-alkyl,
- (e) nitro,
- (f) hydroxy,
- (g) carboxy,
- (h) $(C_1–C_6)$-alkoxy,
- (i) $(C_1–C_6)$-alkoxycarbonyl,
- (j) aminosulphonyl,
- (k) $(C_1–C_6)$-alkylaminosulphonyl,
- (l) di-$(C_1–C_6)$-alkylaminosulphonyl,
- (m) carbamoyl,
- (n) $(C_1–C_6)$-alkylcarbamoyl,
- (o) di-$(C_1–C_6)$-alkylcarbamoyl,
- (p) trifluoromethyl,
- (q) sulphonic acid,
- (r) amino,
- (s) $(C_1–C_6)$-alkylamino,
- (t) di-$(C_1–C_6)$-alkylmino,
- (u) $(C_1–C_6)$-alkanoylamino,
- (v) $(C_1–C_6)$-alkanoyl(N-$(C_1–C_6)$-alkyl)amino,
- (w) $(C_1–C_6)$-alkanesulphonamido, or
- (x) $(C_1–C_6)$-alkyl-$S(O)_n$ wherein n is 0–2;

comprising the steps of:

(1) charging a solution of carbon dioxide source having a pH range of about 6.0 to about 12.0 into a reaction vessel;

(2) adding an effective amount of a mole ratio of a base and an active ingredient into the reaction vessel containing the solution of carbon dioxide source to maintain pH at about 6.0 to about 9.0 and a temperature range of about −3° C. to about 15° C.;

(3) lyophilizing the solution of Step (2) to yield the final formulation product of a compound of formula I with less than about 10% of moisture content.

2. The process of claim 1, wherein the carbon dioxide source is selected from the group consisting of carbon dioxide, sodium bicarbonate, potassium bicarbonate,

sodium carbonate, potassium carbonate, calcium carbonate, cesium carbonate, magnesium carbonate, lithium carbonate, and a mixture thereof.

3. The process of claim 2, wherein the carbon dioxide source is sodium bicarbonate.

4. The process of claim 3, wherein the carbon dioxide source in Step (1) is present in an amount relative to the amount of active ingredient, wherein a mole ratio of carbon dioxide source to the active ingredient is about 0.5 to about 1.5.

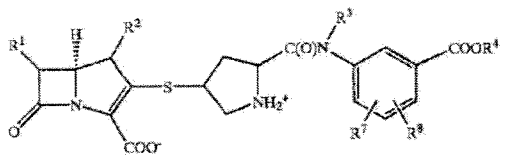
5. The process of claim 4, wherein the carbon dioxide source in Step (1) is present in an amount relative to the amount of active ingredient, wherein a mole ratio of carbon dioxide source to the active ingredient is about 0.8 to about 1.2.

6. The process of claim 5, wherein the pH range in Step (1) is about 7.0 to about 9.0.

7. The process of claim 6, wherein a temperature range in Step (1) is about −3° C. to about 15° C.

8. The process of claim 7, where the active ingredient is a compound of formula (a),

(a)



wherein R^1, R^2, R^3, R^4, R^7 and R^8 are as defined above.

9. The process of claim 8, wherein the base is selected from the group consisting of sodium hydroxide, lithium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide, magnesium hydroxide, lithium methoxide, sodium methoxide, potassium methoxide, calcium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium tert-butoxide, sodium tert-butoxide and potassium tert-butoxide.

10. The process of claim 9, wherein the base is sodium hydroxide at a concentration range of about 1N to about 3N.

11. The process of claim 10, wherein the effective amount of a mole ratio of a base to an active ingredient in Step (2) is about 0.7 to about 1.0.

12. The process of claim 11, wherein the mole ratio of a base to an active ingredient in Step (2) is about 0.8 to about 0.9.

13. The process of claim 12, wherein the pH range in Step (2) is about 7.0 to about 8.0.

14. The process of claim 13, wherein the temperature range in Step (2) is about −1° C. to about 5° C.

15. The process of claim 14, wherein the base is added followed by the addition of the active ingredient in Step (2).

16. The process of claim 15, wherein the temperature range in Step (2) is about −1° C. to about 5° C.

17. The process of claim 16, wherein the Step (2) further comprises a titration of the solution using a titrating agent to maintain the pH of the solution at a range of about 6.5 to about 8.5.

18. The process of claim 17, wherein the titrating agent is selected from the group consisting of sodium hydroxide, lithium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide, magnesium hydroxide, lithium methoxide, sodium methoxide, potassium methoxide, calcium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium tert-butoxide, sodium tert-butoxide and potassium tert-butoxide.

19. The process of claim 18, wherein the moisture content of the final formulation product is less than about 5%.

20. The process of claim 1, wherein the step (3) initially further comprises the following steps of:

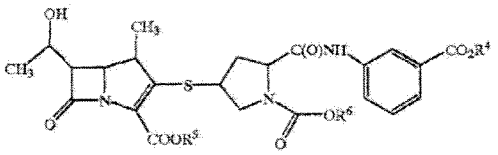
(a) filtering solution of Step 2 into a receiving vessel using a sterilizing filter;

(b) aseptically filling the filtered solution of Step 2 into a sterile vial; and

(c) placing a lyophilization stopper on the filled sterile vial containing the solution of step 2.

21. A process for preparing a final formulation product of a compound of Formula Ia,

Ia



or its pharmaceutically acceptable salt, or hydrates wherein, R^4, R^5, and R^6 are independently:

(a) hydrogen

(b) (C_1–C_6)-alkyl, or

(c) alkali-metal or alkali earth-metal wherein the alkali-metal or alkali earth-metal is sodium, potassium, lithium, cesium, rubidium, barium, calcium or magnesium;

comprising the steps of:

(1) charging a solution of carbon dioxide source having a pH range of about 6.0 to about 12.0 into a reaction vessel;

(2) adding an effective amount of a mole ratio of a base and an active ingredient into the reaction vessel containing the solution of carbon dioxide source to maintain pH at about 6.0 to about 9.0 and a temperature range of about −3° C. to about 15° C.;

(3) lyophilizing the solution of Step (2) to yield the final formulation product of a compound of formula Ia with less than about 10% of moisture content.

22. The process of claim 21, wherein the carbon dioxide source is selected from the group consisting of carbon dioxide, sodium bicarbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, calcium carbonate, cesium carbonate, magnesium carbonate, lithium carbonate, and a mixture thereof.

23. The process of claim 22, wherein the carbon dioxide source is sodium bicarbonate.

24. The process of claim 23, wherein the carbon dioxide source in Step (1) is present in an amount relative to the amount of active ingredient, wherein a mole ratio of carbon dioxide source to the active ingredient is about 0.5 to about 1.5.

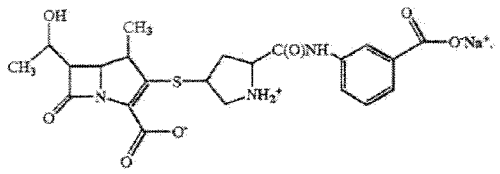
25. The process of claim 24, wherein the carbon dioxide source in Step (1) is present in an amount relative to the amount of active ingredient, wherein a mole ratio of carbon dioxide source to the active ingredient is about 0.8 to about 1.2.

26. The process of claim 25, wherein the pH range in Step (1) is about 7.0 to about 9.0.

27. The process of claim 26, wherein a temperature range in Step (1) is about −3° C. to about 15° C.

28. The process of claim 27, where the active ingredient is a compound of formula (a)',

(a)'



29. The process of claim 28, wherein the base is selected from the group consisting of sodium hydroxide, lithium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide, magnesium hydroxide, lithium methoxide, sodium methoxide, potassium methoxide, calcium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium tert-butoxide, sodium tert-butoxide and potassium tert- butoxide.

30. The process of claim 29, wherein the base is sodium hydroxide at a concentration range of about 1N to about 3N.

31. The process of claim 30, wherein the effective amount of a mole ratio of a base to an active ingredient in Step (2) is about 0.7 to about 1.0.

32. The process of claim 31, wherein the mole ratio of a base to an active ingredient in Step (2) is about 0.8 to about 0.9.

33. The process of claim 32, wherein the pH range in Step (2) is about 7.0 to about 8.0.

34. The process of claim 33, wherein the temperature range in Step (2) is about −1° C. to about 5° C.

35. The process of claim 34, wherein the base is added followed by the addition of the active ingredient in Step (2).

36. The process of claim 35, wherein the temperature range in Step (2) is about −1° C. to about 5° C.

37. The process of claim 36, wherein the Step (2) further comprises a titration of the solution using a titrating agent to maintain the pH of the solution at a range of about 6.5 to about 8.5.

38. The process of claim 37, wherein the titrating agent is selected from the group consisting of sodium hydroxide, lithium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide, magnesium hydroxide, lithium methoxide, sodium methoxide, potassium methoxide, calcium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium tert-butoxide, sodium tert-butoxide and potassium tert- butoxide.

39. The process of claim 38, wherein the moisture content of the final formulation product is less than about 5%.

40. The process of claim 21, wherein the step (3) initially further comprises the following steps of:

(a) filtering the solution of Step 2 into a receiving vessel using a sterilizing filter;

(b) aseptically filling the filtered solution of step 2 into a sterile vial; and

(c) placing a lyophilization stopper on the filled sterile vial containing the solution of Step 2.

* * * * *

CERTIFICATE OF SERVICE

I hereby certify that the foregoing Brief of Plaintiff-Appellant Merck Sharp & Dohme Corp. was served on the following counsel of record in this matter through the CM/ECF system for the U.S. Court of Appeals for the Federal Circuit this 22nd day of December, 2016:

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CERTIFICATE OF COMPLIANCE

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